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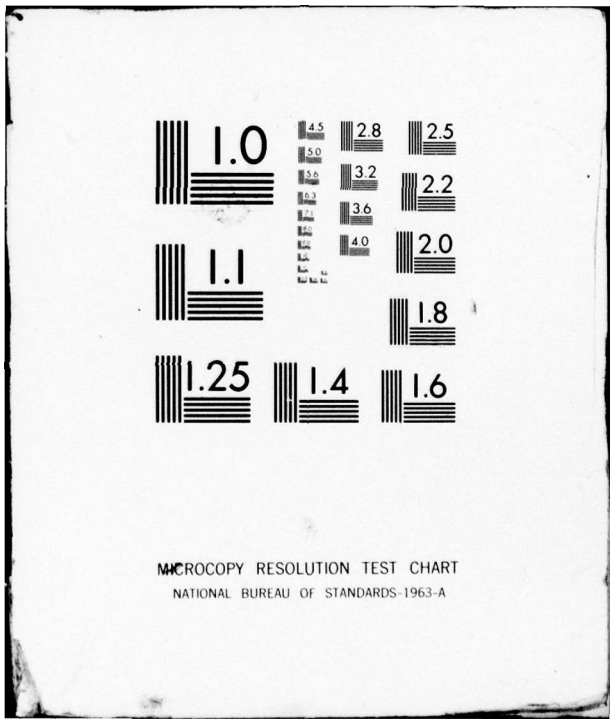
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# CLINICAL INVESTIGATION SERVICE

# ANNUAL RESEARCH PROGRESS REPORT

# FISCAL YEAR 1979










## MADIGAN ARMY MEDICAL CENTER

## TACOMA, WASHINGTON 98431

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

## REPORT DOCUMENTATION PAGE

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Clinical Investigation Service
Madigan Army Medical Center
Tacoma, Washington 98431

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Tacoma, Washington 98431

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18. SUPPLEMENTARY NOTES

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Unit summary; research protocols (objective, method, progress, status); publications; presentations.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Subject report identifies those individuals who are conducting investigative protocols at Madigan Army Medical Center. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented.

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REPORTS CONTROL SYMBOL MED-300

# ANNUAL PROGRESS REPORT

30 SEPTEMBER 1979

CLINICAL INVESTIGATION SERVICE

MADIGAN ARMY MEDICAL CENTER

TACOMA, WASHINGTON 98431

ANNAUL RESEARCH PROGRESS REPORT

FISCAL YEAR 1979

CLINICAL INVESTIGATION SERVICE
MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council, and the Guiding Principles in the Care and Use of Animals (Appendix I), approved by the Council of the American Physiological Society. The investigators follow the recommendations from the Declaration of Helsinki (Appendix II) in the performance of investigations involving human subjects.

***

CODE:

C - Completed
O - Ongoing
T - Terminated
P - Publication
PR - Presentation
SP - Submitted for publication

Work unit Number: 79*/01**

* - Fiscal year in which registered
** - Chronological order of registration

## FOREWORD

The staff at Clinical Investigation Service would like to take this opportunity to express their appreciation to the staff of MAMC for their willingness to support and cooperate in the performance of our research mission. We would also like to thank all the investigators who replied to our request for an abstract promptly and who obviously gave some thought to the preparation of their material.

This report reflects the integration of Clinical Investigation Service and the clinical staff of Madigan Army Medical Center in investigative endeavors. It is through investigation and the willingness to accept new thoughts that the advancement of medical care can be made possible. Research endeavors should be viewed as an ongoing process of continuing medical education for the investigators, volunteers, and, finally, those individuals who are made aware of the conclusions which can be drawn from the research. It is pointed out that the process of developing a research protocol is informative and educational for all those individuals who are involved in this process and that a completed protocol is not necessarily and indication of knowledge gained. At times, the largest portion of the educational experience in a research endeavor is in the initial preparation.

The research protocols described in this report were conducted under the provisions of AR 40-38, Clinical Investigation Program, AR 70-25, Use of Volunteers as Subjects of Research, and MAMC Supplement 1 to AR 40-38, Medical Services Clinical Investigation Program. Readers of this report are reminded that many of these abstracts are preliminary and are not to be construed as the final report or necessarily the end result of the protocol.

A great deal of effort went into the preparation of this report. I would like to express my appreciation to Ms. Nancy Whitten for the effort that she extended in the compilation of this report.

Bruce L. Fariss

BRUCE L. FARISS, M.D.
COL, MC
Chief, Clinical Investigation Service

## UNIT SUMMARY FY 79

1. Objective

To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan Army Medical Center.

2. Technical Approach

MANPOWER

| DESCRIPTION | RANK | MOS |
|---|---|---|
| Chief<br>Fariss, Bruce L., MC | 06 | 61C9A |
| Assistant Chief<br>Plymate, Stephen R., MC | 05 | 61C9B |
| Vet Lab Officer<br>Ward, George S., VC | 04 | 64C00 |
| Bacteriologist<br>Crumrine, Martin H., MSC | 04 | 68A9C |
| Physiologist<br>Jacob, Willis H., MSC | 04 | 68J9C |
| Biochemist<br>Smith, Michael L., MSC | 03 | 68C9C |
| NCOIC<br>Garretson, Charles | E6 | 92B40 |
| Med Lab Spec<br>Darrow, Robert | E5 | 92B30 |
| OR Tech<br>Gold, Joy | E5 | 91D20 |
| Vet Anim Spec<br>Lee, Donald R. | E4 | 91T20 |
| Vet Anim Spec<br>Pack, Donald L. | E4 | 91T20 |
| Vet Anim Spec<br>Kelley, Katherine | E3 | 91T20 |

| DESCRIPTION | RANK | MOS |
|---|---|---|
| Med Tech, Supervisor<br>Graves, James N. | GS9 | 00644 |
| Med Tech<br>Garrison, Mina J. | GS7 | 00644 |
| Med Tech<br>Matej, Louis A. | GS7 | 00644 |
| Edit Asst/Steno<br>Whitten, Nancy J. | GS6 | 00318 |
| Clerk Steno<br>Fraser, Elizabeth L. | GS4 | 00312 |
| Animal Caretaker<br>Mallouf, Jerry L. | WG6 | 07706 |

| | FUNDING |
|---|---|
| MEDCASE Equipment | $53,424.73 |
| Capital Equipment | 1,673.64 |
| Personnel Services (Civilian salaries) | 93,232.47 |
| Consumable Supplies | 39,013.47 |
| Contractual Services | 867.22 |
| TOTAL | $188,211.53 |

3. Progress

During FY 79 there were 147 active protocols. Of these, 90 are presently ongoing; 22 completed; and 37 terminated. In addition, administrative work has been done on 51 protocols that are pending final approval from HSC or OTSG.

There were 23 publications, 12 papers have been accepted for publication, 17 papers have been submitted for publication, and there were 19 presentations.

4. Committe Members

Commander
Madigan Army Medical Center

BG William R. Dwyre, MC

CLINICAL INVESTIGATION COMMITTEE

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## PRESENTATIONS FY 79

### CLINICAL INVESTIGATION SERVICE

Jennings, P.B., Knudson, R.P., Alden, E.R., and Crumrine, M.H.: Evolution and Evaluation of a Heel-Stick Blood Culture Technique for Neonatal Use (Exhibit). American Academy of Pediatrics, Chicago, IL, Oct 78. Gold Medal Award.

Lowell, G.H., Fischer, G.W., Wilson, S.R., and Crumrine, M.H.: Serum from Adults Immunized with Pneumococcal Vaccine is Opsonic *in vitro* and Protective *in vivo* for Group B Type III Streptococci. The Society for Pediatric Research, Univ of New Mexico, 4 May 79. Paper #936.

Luqman, W.A., Saunders, C.G., and Smith, M.L.: A Fetal Weight Determinant Based on Maternal Glycemia and Positive Caloric Balance in Non-Diabetic Pregnant Women. 17th Annual Meeting of the Armed Forces District of American College of OB GYN and 27th Armed Forces Seminar (combined meeting), Washington, DC, 15-19 Oct 78.

Luqman, W.A. and Smith, M.L.: Maternal Glycemia and Birth Weight - A Spectrum Not a Syndrome. Annual Meeting of the American Association for the Advancement of Science, Houston, TX, Jan 79.

Luqman, W.A.: Seminal Immunoreactive Prolactin. 6th National Institute of Child Health and Human Development Workshop on the Testis, Houston, TX, 13-16 Mar 79.

Luaman, W.A.: The Biochemical Basis of Endocrine Disorders. University of Houston at Clear Lake City, Houston, TX, 14 Mar 79.

Smith, M.L. and Luqman, W.A.: Correlation Between Sperm Count and Semen Prolactin Levels in Humans. Annual Meeting of the American Association for the Advancement of Science, Houston, TX, 3-8 Jan 79.

Smith, M.L., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Post Vasectomy Subjects. 7th Biennial International Conference, Endocrinology '79, London, Jul 79.

PRESENTATION (Cont)

Clinical Investigation Service (Cont)

Ward, G.S.: Comparative and Experimental Abdominal Surgery. Univ of Washington, Div of Lab Animal Medicine, Residency Training Program, Seattle, WA, 9 Jan 79.

Ward, G.S.: Comparative and Experimental Cardiovascular Surgery. Univ of Washington, Div of Lab Animal Medicine, Residency Training Program, Seattle, WA, 23 Jan 79.

Ward, G.S.: Asepsis and Surgical Procedures. Univ of Washington, Dept of Physiology and Div of Lab Animal Medicine, Seattle, WA, 13 Feb 79.

## DEPARTMENT OF FAMILY PRACTICE

Fitzgerald, R.D.: The Use of Group Process in Teaching Family Dynamics to Family Practice Residents. Annual Meeting of American Association for Marriage and Family Therapy, Houston, TX, 13 Oct 78.

## DEPARTMENT OF MEDICINE

Pierce, H.I.: Reappraisal of the Clinical Usefulness of Red Blood Cell Counting Parameters. Annual Meeting of the Clinical Laboratory Physicians and Scientists, Dartmouth-Hitchcock Medical Center, Hanover, NH, 30 May-1 Jun 79.

## DEPARTMENT OF PATHOLOGY

Keniston, R.C., Smith, M.L., and Matej, L.A.: Role of Vitamin B6 and Putrescine in Human Lymphocyte Activation: Beneficial Effect on Dietary Vitamin B6 Supplements. Joint Meeting, British Columbia Society of Clinical Chemists and American Association for Clinical Chemists (NW Section), Harrison Hot Springs, BC, 20-22 Sep 79.

Valeri, C.R. and Roth, R.R.: Cryopreservation of Platelets. 4th Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists, Seattle, WA, 11 Oct 78.

PRESENTATIONS (Cont)

## DEPARTMENT OF PEDIATRICS

Atkinson, A.W., Tuttle, W., Toews, W.H., and Wynder, S.: Pediatric Nuclear Cardiology (Exhibit), American Academy of Pediatrics, Chicago, IL, Oct 78. Bronze Medal for Excellence in Teaching Value.

Atkinson, A.W., Tuttle, W., Toews, W.H., and Wynder, S.: Pediatric Nuclear Cardiology. American College of Cardiology, Miami, FL, 11-14 Mar 79.

## DEPARTMENT OF SURGERY

Camp, R.A., Weatherwax, R.J., and Miller, E.B.: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint. American Society for Surgery of the Hand, San Francisco, CA, 18-23 Feb 79

## SOCIAL WORK SERVICE

McKain, Jerry L: Violence in Military Families: A Study of the Correlation Between Interpersonal Isolation, Change, and Family Violence. Purdue University Conference on Family Violence, W Lafayette, IN, 26 Feb 79.

## PUBLICATIONS FY 79

### CLINICAL INVESTIGATION SERVICE

Crumrine, M.H., Fischer, G.W., and Balk, M.W.: Immunochemical Cross-Reactions Between Type III Group B *Streptococcus* and Type 14 *Streptococcus pneumoniae*. Infect Immun 25:960-63, 1979.

Crumrine, M.H.: Detection of Bacterial Antigens by Counterimmunoelectrophoresis. Proceedings of the 4th Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists. (Abstract)

Fischer, G.W., Crumrine, M.H., Lowell, G.H., and Wilson, S.R.: Immunoprecipitation and Opsonic Cross-Reaction Between Type-14 *Pneumococcus* and Group-B *Streptococcus* Type III. Lancet 1(8107): 75-77, 13 Jan 79.

Gandara, D.R. and Fariss, B.L.: Persistence of Periodic Paralysis Following Treatment of Thyrotoxicosis. Mil Med 144:337-38, 1979.

Heggers, J.P., Robson, M.C., Yetter, J.F., Krieg, R.W., and Jennings, P.B.: Tumoricidal Effects of *Mycobacterium ulcerans* Toxins on Murine Adenocarcinoma (C3HBA). J Surg Oncology 11: 161-69, 1979.

Luqman, W.A. and Smith, M.L.: Seminal Radioimmunoreactive Prolactin Before and After Vasectomy. Clin Endocrinol 10:213, 1979.

Luqman, W.A., Sakakini, J., Rakoff, J.S., Saunders, C.G., Moore, W.J., Smith, M.L., and Tuttle, W.K.: A Fetal Weight Determinant Based on Maternal Glycemia and Positive Caloric Balance in Non-Diabetic Pregnant Women. Abstracts of the Armed Forces District of American College of OB GYN, Oct 78.

Luqman, W.A. and Smith, M.L.: Maternal Glycemia and Birth Weight - A Spectrum Not a Syndrome. Abstracts of the Annual Meeting of the American Association for the Advancement of Science, Jan 79. Abstract #314, p 116.

Luqman, W.A., Smith, M.L., Kulwin, R., Saunders, C., and Moore, W.: Maternal Glycemia and Birth Weight. Abstracts of Endocrinology '79, 7th Biennial Internatl Conf, London, Jul 79, p 77.

Ridgway, R.L. and Zielke, D.R.: Nonsurgical Endodontic Technique for Dogs. JAVMA 174:82-85, 1979.

Smith, M.L., Plymate, S.R., Jacob, W.H., and Luqman, W.A.: Inherent Ranges of Seminal Prolactin in Pre and Post Vasectomy Subjects. Abstracts of Endocrinology '79, 7th Biennial Internatl Conf, London, Jul 79, p 67.

Smith, M.L. and Luqman, W.A.: Correlation Between Sperm Count and Semen Prolactin Levels in Humans. Abstracts of the Annual Meeting of the American Association for the Advancement of Science, Jan 79, Abstract #313, p 116.

Smith, M.L., Luqman, W.A., and Rakoff, J.S.: Correlations Between Semen Radioimmunoreactive Prolactin, Sperm Count and Sperm Motility in Prevasectomy and Infertility Clinic Patients. Fertil Steril 32:312-315, 1979.

Smith, M.L., Luqman, W.A., and Matej, L.A.: Comparison of Prolactin Levels in Human Semen and Seminal Plasma: J Endocrinol 81:131, 1979.

Thomason, A.M. and Fariss, B.L.: The Prevalence of Varicoceles in a Group of Healthy Young Men. Mil Med 144:181-82, 1979.

## DENTAL ACTIVITY

Zielke, D.R., Harrison, J.W., and Heggers, J.P.: An Analysis of the Sensitivity of Non-rereduced PRS Medium in Endodontic Therapy. Oral Surg, Oral Med, Oral Path 47:83-86, 1979.

## DEPARTMENT OF FAMILY PRACTICE

Hollison, R.V., Vasquez, A.M., and Warner, D.H.: A Medical Information System for Ambulatory Care, Research, and Curriculum in an Army Family Practice Residency: 51,113 Patient Problems. J Fam Prac 7:787-95, 1978.

## DEPARTMENT OF MEDICINE

Bass, J.W., Podgore, J.K., and Halstead, S.B.: Booster Immunization with Trivalent Oral Polio Vaccine. JAMA 239:22-52, 1978.

Covelli, H.D. and Wilson, R.T.: Immunologic and Medical Considerations in Tuberculin-Sensitized Pregnant Patients. Amer J Obstet Gynecol 132:256-59, 1978.

PUBLICATIONS FY 79 (Cont)

## DEPARTMENT OF PATHOLOGY

Oberhofer, T.R.: Comparison of the API 20-E and Oxiferm Systems With a Conventional Method in the Identification of Nonfermentative Bacteria. J Clin Microbiol 9:220-26, 1979.

Oberhofer, T.R. and Back, A.E.: Biotypes of Haemophilus Encountered in the Clinical Laboratory. J Clin Microbiol 10:168-74, 1979.

## DEPARTMENT OF SURGERY

Camp, R.A., Weatherwax, R.J., and Miller, E.B.: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint. J Hand Surg 4:286, 1979. (Abstract)

Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. Laryngoscope 88: 1796-1824, 1978.

## ACCEPTED FOR PUBLICATION FY 79

### CLINICAL INVESTIGATION SERVICE

Luqman, W.A., Przasnyski, E.J., McCowen, K.D., and Reed, J.W.: Hypocalcemia in Patients with Cancer: A Review. Military Medicine.

Luqman, W.A., Saunders, C., Moore, W., Smith, M.L., and Kulwin, R.: Third Trimester Glucose Homeostasis and Feto-placental Maturation. American Journal of Obstetrics and Gynecology.

McCowen, K.D., Smith, M.L., Modarelli, R.O. Fariss, B.L., and Reed, J.W.: Tissue Testosterone and Dihydrotestosterone from Bilateral Testis Biopsies in Infertile Males with Varicocele. Fertility and Sterility.

Ridgway, R.L. and Usry, R.T.: Cryopreservation of Platelets Simplified: A Modified Glycerol-Glucose Method. Transfusion.

### DENTAL ACTIVITY

Todd, M.J. and Harrison, J.W.: An Evaluation of the Immediate and Early Sealing Properties of Cavit. Journal of Endodontics.

### DEPARTMENT OF MEDICINE

Nessan, V.J., Jacoway, J.R., Lauttman, R.J., Swintak, E.F., and Buhler, J.E.: Biopsy of Minor Salivary Gland in the Diagnosis of Sarcoidosis. New England Journal of Medicine.

Weled, B.J., Winfery, D., and Downs, J.B.: Technique and Rational for Measuring Exhaled Volume with Continuous Positive Airway Pressure (CPAP) and Intermittent Mandatory Ventilation. Chest.

Zaloznik, A.J. and McCowen, K.D.: Hypokalemic Myopathy with Serum Enzyme Elevations and Failure of Adrenal Scintiscan in a Patient with Adrenal Adenoma. Military Medicine.

Accepted for Publication (Cont)

## DEPARTMENT OF PEDIATRICS

Yokan, C., Turner, C., Knudson, R.P., Stracener, C., and Alden, E.R.: Infant Preventive Care in a Young and Healthy Population. Military Medicine.

## DEPARTMENT OF SURGERY

Camp, R.A., Weatherwax, R.J., and Miller, E.B.: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint. Journal of Hand Surgery.

## PHYSICAL MEDICINE & REHABILITATION SERVICE

Budurowich, M. and Lofton, W.: Occupational Therapy Program for Diabetics. Diabetes Care.

## SOCIAL WORK SERVICE

Fitzgerald, R.D.: The Use of Group Process in the Teaching of Family Dynamics to Family Practice Residents. Journal of Family Practice.

## SUBMITTED FOR PUBLICATION FY 79

### CLINICAL INVESTIGATION SERVICE

Crumrine, M.H., Balk, M.W., and Fischer, G.W.: An Experimental Model of Neonatal Group B Streptococcal Sepsis and Meningitis. Submitted to J Infect Dis.

Friedman, N.M. and Plymate, S.R.: Leydig Cell Dysfunction and Gynecomastia in Adult Males Treated with Alkylating Agents. Submitted to Clin Endocrinol.

Luqman, W.A. and Smith, M.L.: Maternal Glycemia and Birth Weight. Submitted to Int J Obstet Gynecol.

Luqman, W.A. and Smith, M.L.: The Effect of Freezing and Storage on Seminal Immunoreactive Prolactin. Submitted to J Endocrinol Invest.

Luqman, W.A., Smith, M.L., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Post Vasectomy Subjects. Submitted to Int J Fertil.

Luqman, W.A. and Chadband, R.: Malignancy and Paradoxical Secretion of Hormones. Submitted to NEJM.

Luqman, W.A. and Smith, M.L.: Comments on Parameters of Semen Analysis. Submitted to Saudi Medical Journal.

McCowen, K.D., Reed, J.W. and Fariss, B.L.: The Role of Thyroid Suppression in Patients with Thyroid Cyst. Submitted to Amer J Med.

Plymate, S.R., Smith, M.L., Jacob, W.H., and Matej, L.A.: Androgen Binding Protein in Human Seminal Fluid. Submitted to J Clin Endocrinol Metab.

Przasnyski, E.J., Bohman, V.D., and Plymate, S.R.: Cimetidine in Suppression of Gastric Acid Secretion. Submitted to NEJM.

Ward, G.S.: Gastric Trichobezoars in Rabbits. Submitted to VM/SAC

SUBMITTED FOR PUBLICATION (Cont)

## DENTAL ACTIVITY

Harrison, J.W. and Todd, M.J.: The Effect of Root Resection on the Sealing Property of Root Canal Obturations. Submitted to Oral Surg Oral Med Oral Pathol.

## DEPARTMENT OF PATHOLOGY

Oberhofer, T.R. and Podgore, J.K.: *Yersinia pseudotuberculosis:* Use of Cold Temperature Enrichment for Isolation. Submitted to J Clin Microbiol.

Oberhofer, T.R.: Growth of Nonfermentative Bacteria at 42°C. Submitted to J Clin Microbiol.

## DEPARTMENT OF PEDIATRICS

Knudson, R.P. and Alden, E.R.: Neonatal Heelstick Blood Culture. Submitted to Pediatrics.

Ortiz, A., Knudson, R.P., Toews, W.H., and Alden, E.R.: Oxygen Consumption in Infants: The Difference Between Radiant Energy Warmers and Conventional Incubators. Submitted to Amer J Dis Chil.

## DEPARTMENT OF OB/GYN

Sakakini, J: Serum Unconjugated Estriol in Obstetrics, A Review. Submitted to J Repro Med.

# DETAIL SHEETS
# FOR
# PROTOCOLS

TITLE: Characterization of the Antigenic Similarities of Group B Streptococci and *Streptococcus pneumoniae*.

PRINCIPAL INVESTIGATOR: CPT Martin H. Crumrine, MSC

PROFESSIONAL ASSISTANTS: LTC Errol R. Alden, MC
LTC John K. Podgore, MC

WORK UNIT NO: 78/48

## TECHNICAL OBJECTIVE

To further delineate the antigenic similarities between type III Group B streptococci and *Streptococcus pneumoniae*.

## METHOD

1. To isolate and purify GBS antigens and *Pn.* antigens.
   a. Organisms will be cultured in a chemically defined medium.
   b. Antigens will be extracted, using several techniques, and fractionated.
   c. Protein DNA and RNA will be removed from the carbohydrate antigens.
   d. The antigen then will be concentrated by lyophilization.
2. The following antibodies will be produced in rabbits.
   a. Whole cell GBS and *Pn.* antibody.
   b. Antibodies against each of the type specific whole cell antigens of the 5 types of GBS and several pneumococcal types.
   c. Antibodies against various type specific polysaccharides.
3. Comparisons of all 5 GBS types with various *Pn.* antisera and *Pn.* antigens with GBS type specific antisera and GBS whole cell antisera using the following techniques: immunodiffusion, chemiluminescence, opsonophagocytic activity, and animal protection tests.
4. To characterize the cross reactive antigenic sites using specific mono- and oligosaccharides to demonstrate the similarities of the antigenic sites.
5. To determine if any cross reactive antigens are in the pneumococcal vaccine using the techniques described above.

## PROGRESS

(78 10 - 79 09) Electrophoresis equipment necessary for this project arrived in Aug 79, thus progress has been limited.

STATUS: (O)

TITLE: Renal Glycosuria: Evaluation of Renal Function, Carbohydrate Metabolism and Possible Development of Diabetes Mellitus

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 69/01

## TECHNICAL OBJECTIVE

To study patients with renal glycosuria in an attempt to further classify these patients. More importantly, we shall attempt to distinguish those patients who may develop diabetes mellitus by studying responses to oral glucose and intravenous glucose and tolbutamide with measurement of blood and urine glucose and insulin levels. The patients will be reevaluated at yearly intervals up to five years to determine the incidence of diabetes mellitus.

## METHOD

Forty patients who are found to have flat or normal oral glucose tolerance tests with renal glycosuria shall be evaluated.

Day 1: History, physical examination, routine CBC, chest x-ray, STS, regular hospital diet (300 gm CHO).

Day 2: Twenty-four hour urine for Na, K, $CO_2$, $Cl_2$, Ca, P, SGOT, alkaline phosphatase, BUN, creatinine, uric acid and serum electrophoresis. Urinary pH measured at each voiding.

Day 3: Oral glucose tolerance blood and urine glucose and plasma insulin levels.

Day 4: Intravenous glucose tolerance test (25 gm), blood and urine glucose and plasma insulin.

Day 5: Infusion of glucose, intravenous to calculate the splay (renal tubular reabsorption as a function of lead presented to the tubule). Inulin and endogenous creatinine clearances to be done in conjunction with the glucose infusion.

Day 6: Day of rest.

Renal Glycosuria - Fariss

Day 7: Tolbutamide tolerance test (1.0 gm I.V.) specimens for glucose and insulin at 0, 2, 15, 30, 45, 60, 90, 120, 150, and 180 minutes.

Day 8, 9, and 10: $NH_4Cl$ loading p.o. with measurement of hydrogen secretory capacity, net acidification and ammonia production each day.

PROGRESS

(78 10 - 79 09) To date, two patients of this group of 39 individuals, have developed diabetes mellitus. There are no distinguishing features to indicate that these two individual's preliminary tests were different from the remainder of the group.

STATUS: (O)

TITLE: The Effects of Chronic Hyperglycemia on Pregnancies and Fetuses in Sheep During Gestation

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ George S. Ward, VC

WORK UNIT NO: 74/06

## TECHNICAL OBJECTIVE

The objectives of this project are to determine the effect of hyperglycemia upon pregnancies as manifested by frequency of abortions and hydramnios and possible developmental abnormalities of the fetuses.

## METHOD

The study will be composed of three groups of pregnant ewes with as close proximity of the date of conception as possible. All groups will be given food and water ad lib.

1. The control group will be comprised of six animals with no treatment.

2. Group #2 will be composed of seven animals which have undergone subtotal pancreatectomy. The diabetes mellitus produced surgically will be managed by the injection of intermediate acting insulin such as NPH. Blood sugars will be monitored frequently as indicated clinically.

3. The third group will be composed of seven animals which have indwelling catheters for infusion of hypertonic sugar solutions with a lambda infusion system. The systems are portable, weighing less than 3 lbs and can be strapped to the backs of the animals without difficulty. Blood sugars will be monitored at frequent intervals with an attempt to keep blood sugars between 200 and 300 mg/100 ml of blood at all times.

The course of the pregnancies will be observed for each group of animals. Blood sugars for each group will be determined at frequent intervals during the gestation. At delivery the neonate will be examined pathologically for evidence of pulmonary, liver, pancreatic, kidney, and possible developmental abnormalities.

The Effects of Chronic Hyperglycemia - Fariss

PROGRESS

(78 10 - 79 09) Further pancreatectomies are being performed. Other sheep are being treated with diatogenic drugs. Post-treatment levels for glucagon, glucose, and insulin are being determined.

STATUS: (O)

TITLE: Evaluation of the Cyclic Nature of Human Semen Content

PRINCIPAL INVESTIGATOR: CPT Willis H. Jacob, MSC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
Robert Modarelli, M.D., LTC, MC (Ret)

WORK UNIT NO: 78/34

## TECHNICAL OBJECTIVE

To determine semen quality by measuring sperm count, sperm motility, sperm morphology, and various constituents of seminal fluid. These findings will then be analyzed for cyclic patterns.

## METHOD

1. Test Subjects: Twenty to thirty healthy volunteers will be selected from the 9th Infantry Division or the 62nd Medical Group. Selection will be based on physical examination and medical history. Individuals will be excluded from the project for any of the following reasons: evidence of active venereal disease; a history of testicular varicocele; currently using the sauna on a regular basis; currently taking any medication; any adverse finding during the physical examination. Volunteers will abstain from the use of alcohol and other drugs throughout the semen collection phase of the project. Volunteers will abstain from sexual intercourse for a period beginning 48 hours before collection of the first semen sample and extending throughout the sample collection period.

2. Semen Collection and Analysis: Semen samples will be collected daily for a period of 20 to 25 days. Samples will be collected during a specified 30-minute period each day. The semen, obtained through masturbation, will be ejaculated directly into plastic containers which are free of trace metals. The samples will be allowed to liquefy for one hour at room temperature (240°C). The liquefied samples will be measured for volume and color, and then will be divided into two portions. One portion will be assayed immediately for viscosity, sperm count, sperm motility, and sperm morphology. The other portion of the samples will be centrifuged and the sperm-free seminal fluid will be retained for assay of seminal fluid constituents to include prostaglandins, gonadotropins, trace metals, and carbohydrates.

Evaluation of the Cyclic Nature of Human Semen Content - Jacob

PROGRESS

(78 10 - 79 09) To date, two men have been evaluated for 20 days and one has been evaluated for 15 days. These initial findings suggest that daily variations occur in sperm density, semen volume, total count, PGE, PGF-2$\alpha$, fructose, acid phosphatase, and semen zinc. However, it is not yet possible to clearly define the cyclic nature of these patterns, if a cycle exists. These data will be presented at the Pacific Coast Fertility Society in October 1979. An additional group of 12 men is expected to enter the study in October 1979.

STATUS: (O)

TITLE: Correlation of the Effects of Semen Sperm Count and Prostaglandin Content on Fertility in Human Males

PRINCIPAL INVESTIGATOR: CPT Willis H. Jacob, MSC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
MAJ Jeffrey S. Rakoff, MC
Robert Modarelli, M.D., LTC, MC (Ret)

WORK UNIT NO: 78/45

## TECHNICAL OBJECTIVE

To compare the semen quality of men of known fertility to that of men who are apparently infertile. The parameters of semen quality will be sperm count, sperm motility, sperm morphology, sperm viability, seminal prostaglandins, seminal fructose, seminal zinc, seminal gonadotropins, and gonadal steroids. Seminal prostaglandin content will be compared with each of these parameters.

## METHOD

Semen specimens will be collected from 20-25 volunteers of known fertility and from 20-25 volunteers with apparent infertility. Following a urological evaluation, each volunteer will be asked to provide three semen specimens. Each volunteer will provide a semen specimen following a 48-hour period of abstinence from sexual activity. Subsequent samples, obtained at the end of a 48-hour abstinence period, will be given at one-week intervals for a two-week period. Each volunteer will ejaculate directly into a plastic container which is free of trace metals. The specimens will be analyzed for volume, color, sperm count, sperm motility, sperm morphology, prostaglandins E, prostaglandins F, and various other seminal fluid constituents. The prostaglandin content will be compared with the sperm analysis for correlation. Prostaglandin content will also be compared to other seminal fluid components such as fructose, zinc, gonadotropins, and gonadal steroids.

## PROGRESS

(78 10 - 79 09) Sixteen fertile men have now completed the study and it is anticipated that all fertile volunteers will have completed the study by December 1979. Potential infertile volunteers are being screened and identified by the Infertility Clinic.

STATUS: (O)

TITLE: Testicular Function in Males Treated with Alkylating Agents

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: LTC Friedrich H. Stutz, MC
LTC K. David McCowen, MC
LTC H. Irving Pierce, MC
CPT Michael L. Smith, MSC

WORK UNIT NO: 79/08

## TECHNICAL OBJECTIVE

To evaluate the Leydig cell function of patients treated with alkylating agents.

## METHOD

Baseline levels will be drawn in the morning for serum LH, FSH, testosterone, estradiol, dihydrotestosterone, prolactin, hematocrit, and WBC. Levels will be measured in ten normal males who are being treated with alkylating agents and ten males who are at least three months past their treatment with alkylating agents to allow recovery from the acute effects of restoration of spermatogenesis. All measurements will be drawn on the baseline serum with a sample drawn every 15 minutes for three collections and the serum pooled. Semen for analysis will be collected by masturbation and the sperm profile for prolactin, testosterone, dihydrotestosterone, and androgen binding protein will be measured.

## PROGRESS

(78 11 - 79 09) Technical work on the project has been completed and a paper is being prepared from the data to be submitted to Clinical Endocrinology.

STATUS: (C)

TITLE: Incidence of Hypothermia in Diabetic Ketoacidosis

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: CPT Martin Bassett, MC
Lisa Taylor, M.D.

WORK UNIT NO: 79/56

## TECHNICAL OBJECTIVE

To determine the incidence, severity, and predisposing factors contributing to the development of hypothermia in diabetic ketoacidosis.

## METHOD

Patients at both Virginia Mason Hospital, Seattle, WA, and Madigan Army Medical Center will be utilized, producing a subject population of approximately 50 DKA cases.

Investigators will be notified of all admissions with a diagnosis of DKA within 24 hours. In cases of hypothermia, clinical evaluation for any other underlying causes including recording of ambient temperatures during the time the patient developed symptoms and on arrival to the hospital; history of cold exposure; drug and alcohol history; presence of sepsis or metabolic disturbances potentially accounting for the state.

The procedure outlined below will be followed:

1. Monitoring of accurate temperatures with the use of a hypothermic thermometer hourly on all patients admitted in DKA over a one-year period.

2. Clinical assessment of these patients in regard to the factors contributing to their hypothermia.

3. Correlation of hypothermia with both biochemical and clinical parameters monitored during the treatment of DKA.

4. Descriptive and statistical analysis of the data thus obtained.

5. All data collection will be from histories and lab procedures that are done routinely in the treatment of DKA.

Incidence of Hypothermia - Plymate

PROGRESS

(79 01 - 79 09) To date, 20 patients have been entered on the study and data have been collected.

STATUS: (O)

TITLE: Effects of Prolactin on Seminiferous Tubule Function

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANT: MAJ George S. Ward, VC

WORK UNIT NO: 79/69

## TECHNICAL OBJECTIVE

Both high and low prolactin levels have been shown to influence sperm production. Since no human model is available for studying both of these situations in the same individual, the purpose of this protocol is to evaluate the effects of high and low dose prolactin on seminiferous tubule function of the male rat.

## METHOD

Thirty male post-pubertal rats are to be studied with 10 rats in each group. Photoperiod will be maintained at 14 h light and 10 h dark. Baseline testicular biopsy for morphology, testosterone, dihydrotestosterone, and androgen binding protein will be done along with serum testosterone, dihydrotestosterone, prolactin, LH, FSH, and estradiol. Ten adult rats will then be placed on 2-bromo-α-ergocryptine, 120 mg subcutaneous in oil q.d.; ten will be given cimetidine, 1 mg subcutaneously b.i.d.; and ten will be given saline subcutaneously q.d. and used as controls. After six weeks the animals will be rebiopsied and serum drawn for the previously mentioned studies. After six weeks rest, the treatment groups will be switched with the first group that was on bromocriptine being put on cimetidine and those that were on cimetidine being put on bromocriptine. Prior to being remedicated, blood will again be drawn and biopsies performed. Following this six-week period, blood will again be drawn and biopsies performed. Plasma testosterone, DHT, and androgen binding protein will be measured by the method of Plymate, et al; LH, FSH, and prolactin will be measured by rat RIA NIAMMD materials.

## PROGRESS

(79 03 - 79 09) Sixty (60) animals have completed the study. Of the initial 20 analyzed, there is a significant difference in the pre and post samples of androgen binding protein in the epididymis ($p=.003$). The difference in the testicle was also significant ($p=.001$).

STATUS: (O)

TITLE: Zinc, Copper, Arginine, Carnitine and Total Proteolytic Enzyme Concentrations in the Seminal Fluid of Infertile Patients

PRINCIPAL INVESTIGATOR: CPT Michael L. Smith, MSC

PROFESSIONAL ASSISTANTS: COL James W. Reed, MC
LTC K. David McCowen, MC
MAJ George Brannen, MC
CPT Michael Greer, MC
James Graves, MT (ASCP)
Mina Garrison, MT

WORK UNIT NO: 77/76

## TECHNICAL OBJECTIVE

To measure the concentration of several components in the semen of a population of fertile and infertile patients and to compare the values. This information will add to our understanding of the role of these elements and compounds in fertility and may help in the management of infertile patients. A finding of abnormal values may also yield diagnostic tests for specific fertility problems.

## METHOD

Semen will be collected from at least thirty patients who have fathered a child and these patients will be considered fertile and used as controls. Samples will also be collected from 30 patients whose wives have had a favorable OB-GYN checkup, but the couple cannot conceive. These patients will constitute an infertile population. A sperm count, motility, volume, viscosity, and morphology will be established for each sample one hour after collection. The samples will be frozen at -70°C, and the zinc, copper, arginine, carnitine, and proteolytic enzyme concentration will be determined at a convenient time. When all data are collected, the mean values for the fertile group will be compared with those of the infertile group.

## PROGRESS

(78 10 - 79 09) In the process of investigating the components of seminal plasma listed in the title, we found that some seminal fluid pituitary hormones and steroids correlated with fertility parameters. The resulting publications and presentations are listed below. Further research will continue under another protocol.

Zinc, Copper, Arginine, Carnitine and Total Proteolytic Enzyme Concentrations - Smith

PUBLICATIONS:

Smith, M.L., Luqman, W.A., and Matej, L.: Comparison of Prolactin Levels in Human Semen and Seminal Plasma. J Endocrinology 81: 131, 1979.

Luqman, W.A. and Smith, M.L.: Seminal Radioimmunoreactive Prolactin Before and After Vasectomy. Clin Endocrinol 10:213, 1979.

Smith, M.L., Luqman, W.A., and Rakoff, J.S.: Correlations Between Semen Radioimmunoreactive Prolactin, Sperm Count, and Sperm Motility in Prevasectomy and Infertility Clinic Patients. Fertil Steril, in press.

Luqman, W.A. and Smith, M.L.: The Effect of Freezing and Storage on Seminal Immunoreactive Prolactin. J Endocrinol Inves, in press.

Luqman, W.A., Smith, M.L., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Post Vasectomy Subjects. Inter J Fertil, in press.

PRESENTATIONS AND ABSTRACTS:

Smith, M.L. and Luqman, W.A.: Correlation Between Sperm Count and Semen Prolactin Levels in Humans. Annual Meeting of The American Association for the Advancement of Science, Houston, TX, Jan 79, Abstract #313.

Luqman, W.A. and Smith, M.L.: Hormones in Semen. 1st SEAP Congress of Clinical Biochemistry, Republic of Singapore, May 79.

Smith, M.L., Luqman, W.A., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Post Vasectomy Subjects. Endocrinology '79, 7th Biennial International Conference, London, England, Jul 79, Abstract #79.

STATUS: (C)

TITLE: Polyamines as Chemical Markers of the Response of Patients Being Treated for Cancer

PRINCIPAL INVESTIGATOR: CPT Michael L. Smith, MSC

PROFESSIONAL ASSISTANTS: COL Joseph J. Sakakini, MC
LTC Friedrich H. Stutz, MC
LTC Donald Kull, MC
LTC Dick R. Smith, MC
MAJ Patrick Kronmiller, MC
CPT Carl F. Cricco, MC
CPT Richard Kenniston, MC
SP5 Debbra Naegle
Louis Matej, MT

WORK UNIT NO: 78/25

## TECHNICAL OBJECTIVE

Studies suggest that following urinary polyamine levels can be an effective way to monitor patients under treatment for cancer. Our objective is to obtain pre-, during, and post-treatment urinary polyamine levels on patients with various cancers undergoing various methods of treatment and to correlate these levels with the patient's progress.

## METHOD

Patients: The population of patients will be all consenting cancer patients undergoing chemotherapy, surgery, or radiation therapy. The group will also include benign tumor patients undergoing surgery.

Sample Collection: 24-hour urines will be collected in plastic urine bags containing 10 ml of concentrated HCl. Chemotherapy patients: samples will be collected before treatment, between the first and second treatments, and 10-20 days after the second treatment. Surgery and radiation patients: samples will be collected before treatment, 3-7 days post treatment, and 10-20 days post treatment. Three samples will be collected from each patient and a determination of the creatinine performed. An aliquot will be frozen for polyamine analysis.

Assay: The assay method will be developed concomitantly with sample collections and will include overnight hydrolysis in HCl, extraction with butanol, separation of dansyl derivatives by thin layer chromatography, and individual quantitation by fluorescent densitometry.

Polyamines as Chemical Markers - Smith

Analysis of Results: Urinary polyamine levels will be charted for each patient to determine: if pretreatment levels are above normal; what the levels are during treatment; if the levels return to normal after treatment; and if the trends in the levels indicate effective treatment when compared with the clinical signs and follow-up of the patient.

## PROGRESS

(78 10 - 79 09) A high voltage electrophoresis method and a fluorescent thin layer chromatographic method were developed for the measurement of polyamines in serum and urine. Coinvestigators from the University of Oregon Medical School developed a sensitive radioimmunoassay method for two of the polyamines in both urine and serum. No patients were placed on the protocol from March 1978 through February 1979 so the protocol was terminated.

STATUS: (T)

TITLE: Semen Steroid and Protein Levels in Fertile and Infertile Males

PRINCIPAL INVESTIGATOR: CPT Michael L. Smith, MSC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
MAJ Willis Jacob, MSC
MAJ Wijdan A. Luqman, MC
MAJ Jeffery S. Rakoff, MC
James Graves, MT
Mina Garrison, MT
Louis Matej, MT

WORK UNIT NO: 79/72

## TECHNICAL OBJECTIVE

To measure the levels of testosterone, dihydrotestosterone, prolactin, LH, FSH, and androgen binding protein in the semen of fertile and infertile men. Semen components which differ between the two groups will be noted. Correlations between components will also be studied.

## METHOD

1. Patients: Fertile - 25 prevasectomy patients who have had a child within the past year. Infertile - 50 who have had no children after one year of unprotected intercourse and whose wives meet the following criteria: (a) patent tubes and (b) regular ovulatory menstrual cycles.

2. Two semen samples will be collected from 25 prevasectomy patients prior to vasectomy. One sample will be collected after vasectomy. Three semen samples will be collected from 50 infertile males. Blood samples will also be taken from all patients on the same day that semen is collected. All semen samples for the infertile patients and the postvasectomy samples are part of a routine evaluation. Seminal plasma and serum will be frozen until assayed.

3. Testosterone and dihydrotestosterone levels will be measured on all serum and seminal plasma samples using thin layer chromatography for separation and radioimmunoassay for final analysis.

4. Seminal plasma levels of androgen binding protein will be measured by a $^{3}$H-DHT-polyacrylamide gel method developed by Dr. Plymate. Serum levels of sex binding globulin will be measured by a similar method.

Semen Steroid and Protein Levels in Fertile and Infertile Males - Smith

5. Prolactin, LH, and FSH levels will be measured by a radioimmunoassay method using a kit furnished by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, MD. Prolactin will also be measured by a radioceptor assay using the method of Kennan, et al.

6. After all levels are measured, comparison and statistical analysis will be carried out.

PROGRESS

(79 03 - 79 09) Serum and semen from 70 fertile patients have been collected and assays for 30 of these have been completed. The remainder will be assayed after 1 Oct 79. Information from 50 fertile patients from another protocol will be utilized for comparison. Twenty of these fertile patients have completed all requirements and the remainder will finish by Jan 80. Assays will be completed after Jan 80.

STATUS: (O)

TITLE: Development of Teaching Models for Microvascular Anastomosis, Microneural Reconstruction and Tissue Reimplantation

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/11

## TECHNICAL OBJECTIVE

To develop teaching models for instruction and perfection of residents or staff in the field of microsurgery.

## METHOD

Different species of laboratory animals and anatomical areas will be evaluated to determine which offer the least technical difficulties. Those models which are most successful will then be perfected for end to end and end to side arterial anastomosis. If interest and demand continue, models for microneural reconstruction and tissue reimplantation will also be developed. Various steps will be documented with photography. Contrast radiography will be used to demonstrate vascular patency.

The models developed under this protocol will be used to familiarize residents or other personnel with microsurgical techniques or to refresh staff proficiency prior to clinical application.

## PROGRESS

(78 10 - 79 09) An operating microscope has been obtained and personnel are being familiarized with its usage. Photographic capabilities are now available. Primary emphasis is being placed on perfecting microvascular anastomoses in guinea pig carotid arteries and rat femoral and carotid arteries.

STATUS: (O)

TITLE: Level Of Anesthetic Gases in Local Veterinary Operating Rooms

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
CPT Robert R. Byland, MSC

WORK UNIT NO: 79/11

## TECHNICAL OBJECTIVE

To determine the level of exposure to anesthetic gases by operating room personnel in local veterinary hospitals and to evaluate the efficacy of waste anesthetic gas scavenging systems in use.

## METHOD

Levels of halothane or metophane during scheduled operations under normal conditions will be monitored. If a scavenging system is present, levels will be monitored during its usage and after it is discontinued to determine effectiveness. A Milan Infrared Portable General Purpose Gas Analyzer will be used. If levels of anesthetic gases are consistently too low to be accurately determined by the Milan Gas Analyzer, gas chromatography will be utilized.

## PROGRESS

(78 11 - 79 09) Levels of halothane and/or nitrous oxide have been determined in 14 operating or treatment rooms. Where scavenging devices have been installed, a before and an after value have been determined. Room volume and air flow characteristics have been recorded and correlations or lack thereof will be determined between trace anesthetic levels and methods of delivery or the preceding characteristics. The above determinations have yet to be done in the applicable rooms where metophane is used.

STATUS: (O)

TITLE: Xyladrol Evaluation in the Primate (*Macaca nemestrina*)

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
SP4 Donald R. Lee

WORK UNIT NO: 79/93

## TECHNICAL OBJECTIVE

To determine if Xyladrol, an investigative veterinary pre-anesthetic/anesthetic agent, is potentially addictive, utilizing a morphine addicted pig-tailed macaque as a test animal, and to determine if any toxicity is evidenced at a continuous clinical usage rate.

## METHOD

Phase 1: One monkey will be addicted to morphine and spontaneous withdrawal signs will be noted. Decreasing alleviating doses may be administered as necessary. This phase will allow observing personnel to become familiar with the ten signs of the morphine abstinence syndrome and determination of the dosage of morphine for addiction in the *Macaca nemestrina*. During this phase, a chart will be constructed to grade the degree of withdrawal symptoms.

Phase 2: Six monkeys will be addicted to morphine by the rapid addiction method at a level determined in Phase 1. The maintenance level will probably approach 12-15 mg/kg, which will be given in divided intramuscular doses BID. Substitution for morphine will then be attempted with three test substances. Xyladrol (the formulation utilized throughout this study will be 15 mg xylazine and 5 mg etoxadrol per milliliter) will be administered at the following levels: 0.025; 0.05; 0.1; 0.2; and 0.4 ml/kg. Codeine will be administered in two trials each at: 3, 6, and 12 mg/kg. Saline will be the placebo treatment. Morphine antagonistic effect will also be determined. Three test substances will be used; Xyladrol and saline at the same doses as above, and Levallorphan tartrate (Lorfan-Roche) at 0.05; 0.1 and 0.3 mg/kg. A scoring card or chart will be kept on each monkey for each trial. At least one day on normal morphine maintenance will separate each trial. Menstrual cycles will be monitored and levels of estrogen, FSH, and LH will be determined weekly. LH-RH will be administered at various stages of addiction. The morphine substitution and antagonistic study is required to satisfy FDA suggestions for data to be submitted by development companies. Following the study, addicted monkeys will be gradually weaned by decreasing doses of morphine.

Xyladrol Evaluation in the Primate - Ward

Phase 3: Six different monkeys will be given a clinical dosage of Xyladrol for a period of 21 consecutive days. Clinical signs and evidence of neurological changes or addiction will be noted. Serum chemistries (SMAC) will be done at days 0, 2, 4, 6, 13, and 21. Complete blood counts will be done on days 0, 4, 13, 18, and 21. Urinalysis will be done on days 0, 7, 14, and 21. Ophthalmologic examinations will be done on days 0, 7, 14, and 21. Body weights will be recorded weekly. Menstrual cycles will be monitored and serum estrogen, FSH, and LH will be determined weekly. If changes are noted in any parameters, these will be followed every 14 days for 2-3 months or return to normalcy in 3 monkeys. The other 3 monkeys will continue Xyladrol treatment at increasing doses similar to the rapid morphine addiction schedule to determine if addiction develops. Complete histopathology will be performed on any animals that might expire.

PROGRESS

(79 09 - 79 09) Cages have been ordered. When cages arrive and are installed, monkeys will be ordered. Approximate date to receive monkeys will be 10 Dec 79. Phase I will begin week of 15 Oct 79.

STATUS: (O)

TITLE: The Use of Fluoride and Custom Trays to Treat Dental Hypersensitivity Away From the Dental Office

PRINCIPAL INVESTIGATOR: MAJ Robert Collins, DC

PROFESSIONAL ASSISTANTS: MAJ Kjeld Hansen, C.A.F.
MAJ Lloyd Dixon, DC
LTC Richard Falonski, DC

WORK UNIT NO: 78/19

## TECHNICAL OBJECTIVE

To determine the effectiveness of the utilization of custom trays and a fluoride gel to eliminate or decrease dental hypersensitivity, especially after periodontal srugery, and to evaluate this method for possible future self-treatment by the patient.

## METHOD

Patients who have dental hypersensitivity after periodontal treatment will be screened to reflect surgery in opposite quadrants, either the maxilla or mandible. The patient's base pain threshold will be measured using a thermo-electric tooth stimulator, invented by Dr. M. Ash of the University of Michigan, giving a baseline to measure from. The patient will have a custom tray (made of acrylic) fabricated to his specific oral anatomy of the teeth. Using the custom tray, dental personnel will apply a fluoride gel (strength 2.3%) to the tested site once a day for five minutes. The patient will be measured reference hypersensitivity and verbally questioned every week for one month. A 15 member group using a placebo and the above method will be used as a control. The findings will be accumulated and placed in a graphic/table form for analysis.

## PROGRESS

(78 10 - 79 09) Construction of the power source for the thermo-electric tooth stimulator has been completed. Patient selection is in progress. However, the investigators are having difficulties enlisting a large enough volunteer population so that meaningful results may be obtained.

STATUS: (O)

TITLE: A Radiological Study of Mechanically Produced Lesions in Human Mandibles

PRINCIPAL INVESTIGATOR: MAJ George H. Deitrick, DC

PROFESSIONAL ASSISTANT: COL David Zielke, DC

WORK UNIT NO: 78/23

## TECHNICAL OBJECTIVE

To observe the location and amount of destruction necessary for a lesion in a human mandible to be detectable by dental radiography and to compare results using dry specimens and cadaver mandibles with soft tissue.

## METHOD

Pre-operative photographs and radiographs of mandibles from cadavers; buccal-lingual block sections of mandibles: molar, bicuspid, anterior. Photograph and radiograph each section.

Create periodontal lesions with a #4 round bur; radiograph and photograph interproximal; buccal; lingual; furcation.

Create central bone lesions within block section; radiograph and photograph; remove cancellous bone only; remove buccal-cancellous cortex junction; remove lingual cancellous cortex junction.

Create periapical lesions with a #4 and #8 round bur; radiograph and photograph; extract tooth, create lesion, replace tooth.

Create external lesions with a #8 round bur; radiograph and photograph; 1 mm into buccal plate; ½ way through buccal plate; completely through buccal plate; same for lingual.

## PROGRESS

(78 10 - 79 02) The project is complete. Periapical, central, and peripheral bony lesions were artificially created in four dry human mandibles. The jaws were stabilized and the radiographic technique was standardized. Three dentists interpreted the films.

A Radiological Study of Mechanically Produced Lesions - Deitrick

Periapical lesions of 2-3 mm diameter were visible in the premolar area one-third of the time and in the molar area one-half of the lesions were seen. Central cancellous lesions were rarely observed. Combined cancellous and junction lesions were reported more often than either lesion separately. Cortical destruction produced highly visible lesions.

These findings would indicate that periapical pathosis may be present but not discernable radiographically. Therefore, a thorough endodontic examination using multiple tests should be performed instead of relying too heavily on the radiograph. Central bone pathology may be present without radiographic detection until junctional bone is involved. A high degree of suspicion must be maintained if a central lesion is suspected but not evident on the radiograph. Laminograms may be necessary as a diagnostic aid. Also, it appears that lesions within a child's mandible are more difficult to detect radiographically than in an adult.

Results of the study were presented to the General Dentistry Residency Program to meet requirements of the program. A paper was not prepared for publication as the photographs were lost by the processing company.

STATUS: (C)

TITLE: Modifications of Cavit to Enhance the Immediate Sealing Properties

PRINCIPAL INVESTIGATOR: MAJ David A. Dennis, DC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 79/17

## TECHNICAL OBJECTIVE

Temporary filling materials are used in endodontics to seal the access cavity between treatments. The material selected must provide an effective seal against fluid exchange and salivary contamination of the periapical tissues. The purpose of this study is to evaluate chairside modifications of Cavit (Kerr Manufacturing Company, Detroit, MI) to insure the immediate sealing properties.

## METHOD

Modifications of Cavit to enhance the immediate sealing properties will be investigated by observing the degree of marginal penetration by a 1% solution of methylene blue dye. The study will use 108 extracted single-rooted human teeth. During the time between extraction and the laboratory procedures, the teeth will be stored in a normal saline solution. The apical one-third of each tooth will be removed with a carborundum disk. In the crown of each tooth, a standard lingual access opening will be made and then filled with Cavit or a modified Cavit.

The teeth will be divided into three groups of 36 teeth. Of each group, 12 teeth will be placed into the dye solution immediately (5 minutes post-placement to correspond to clinical time lapse before exposure to saliva); 12 will be placed in normal saline for 6 hours prior to placement into the dye solution; and 12 will be placed in normal saline for 24 hours prior to placement into the dye solution. Of each group of 12, six will be tested by dye at body temperature and six will be thermocycled in the dye. The thermocycle will consist of six cycles for 5 minutes in dye solutions at $4^{o}C$ and $60^{o}C$.

Group I will consist of 36 teeth filled with unmodified Cavit; Group II of 36 teeth filled with Cavit modified by the addition of one drop of water to 5 mm of dispensed Cavit and spatulated for 15 seconds; and Group III of 36 teeth filled with Cavit held under pressure with a moist cotton roll for one minute.

Modifications of Cavit - Dennis

Surface absorption and penetration of the dye through defects in the enamel, dentin, and cementum will be prevented by a coating of sticky wax. Only the restoration and the surrounding 1 mm of tooth surface will be exposed to the dye.

The teeth will be maintained in the dye solution for one hour during the thermocycling or the body temperature solution. After removal from the dye, the teeth will be rinsed for 5 minutes under running water and then embedded in resin. The teeth will be sectioned with a TSM Universal Model 77 Bronwill thin sectioning machine. Serial sections of 500 microns will be obtained and examined under a dissecting microscope for evidence of marginal penetration.

PROGRESS

(78 11 - 79 09) One hundred eight recently extracted anterior teeth were filled with Cavit or Cavit mixed with water or Cavit held under moist pressure. The teeth were immediately immersed into a room temperature dye solution or thermocycled in the dye solution. Under the test conditions, no statistical difference was noted between the test groups based on the marginal penetration of the methylene blue dye.

A presentation of this project was made to the Federal Services Continuing Education Meeting, Fort Lewis, WA, May 1979.

STATUS: (C)

TITLE: Periodontal Diseases: The Relationship Between Immunologic Status and Periodontal Condition

PRINCIPAL INVESTIGATOR: MAJ Lloyd I. Dixon, DC

PROFESSIONAL ASSISTANTS: Leonard C. Altman, MD
Seymour J. Klebanoff, MD
Roy C. Page, DDS

WORK UNIT NO: 78/49

## TECHNICAL OBJECTIVE

The aim of the study is to further the knowledge of the inflammatory response, particularly the accumulation of polymorphonuclear leukocytes and macrophages at sites of microbial invasion or immunologic insult. Advantage will be taken of the association of severe periodontal disease with defects in chemotaxis. Patients with identifiable severe periodontal disease will be evaluated for possible defects in polymorphonuclear leukocytes and macrophage chemotaxis and possible defects in peroxidase mediated microbicidal mechanisms.

## METHOD

Patients age 18-30 displaying radiographic evidence of juvenile periodontitis will be designated as subjects. Normal controls will be volunteer laboratory personnel from the University of Washington. Patients must be in good systemic health with no history of recent treatment with antibiotics, especially tetracycline. The patients will be categorized by age, sex, race, number of teeth affected, mean maximum pocket depth around affected teeth, and a radiographic estimate of the amount of bone loss. 30 cc of whole blood will be drawn from a venipuncture of the median cubital vein and heparinized with 1000 U heparin. A second 10 ml sample will be drawn from the same site and allowed to clot for serum determinations. 5 cc stimulated parotid saliva will be collected using a suction cup and collecting tube from the orifice of Wharton's duct. Blood sample collection will be repeated weekly for a total of three weeks.

Chemotaxis Assay. Polymorphonuclear leukocyte chemotaxis will be examined using a $^{51}Cr$ radiolabelling technique in which patient neutrophils are harvested, labeled with $NA_2\ ^{51}CrO_4$, washed and

placed in the upper compartment of a double micropore filter Boyden chamber. The lower compartment will contain one of three chemotactic attractants (whole human serum activated with endotoxin or zymosan; purified $C_{5A}$). After an incubation of 3 hr, chemotaxis will be determined as cpm of $^{51}Cr$ in the lower filter, corrected for specific uptake of radioactivity by the neutrophils. The mean response of the patient will be expressed as the mean response to each attractant. If no consistent differences are observed among the different attractants, the results will be pooled. Similarly the chemotactic activity generated in the patient's serum will be calculated as a percentage of that observed in normal control study. Random migration of patient or control cells will be determined in chambers containing only buffer in the lower compartment. Microphage chemotaxis will be evaluated in an identical manner, allowing for differences in incubation time and filter pore size diameter.

Standard error will be used throughout as an estimate of variance and means will be compared using student t-test. Nonparametric data will be analyzed by the Fisher exact test. Correlation coefficients will be calculated by linear regression using the method of least squares.

## PROGRESS

(78 10 - 79 09) All clinical data has been collected (10 patients) The data analysis is near completion and a manuscript is in progress.

STATUS: (C)

TITLE: Ultraviolet Photography as a Diagnostic Technique in Detecting Carcinoma

PRINCIPAL INVESTIGATOR: MAJ Richard L. Ferguson, DC

PROFESSIONAL ASSISTANT: COL Wayne Larson, DC

WORK UNIT NO: 77/85

## TECHNICAL OBJECTIVE

To test a recently reported photographic phenomenon (Goldstein, N, et al: Ultraviolet Photography Skin Cancer Diagnosis and Other Clinical Applications. Functional Photography 12:34-37, 1977) for suitability as a reliable, cost effective diagnostic technique.

## METHOD

A two-phase inquiry is planned. The initial part of the plan will deal with attempts to utilize low cost equipment to secure variable ultraviolet return and record comparison exposures on ordinary panchromatic emulsions. Results will be evaluated and a decision made as to proceed with the second phase. The second phase will reproduce the work of Goldstein, utilizing experimental controls and a statistical base. A third phase, assuming a high degree of success in phases I and II, would involve the formulation of an actual clinical diagnostic standard and submission of such a technique for field testing.

## PROGRESS

(78 10 - 79 09) Phase I of the project was completed and one subject was studied. Due to the non-availability of patients who meet the criteria and the departure of the principal investigator, this project has been terminated.

STATUS: (T)

TITLE: Vital Root Retention Below the Height of the Maxillary Alveolous

PRINCIPAL INVESTIGATOR: MAJ Clinton C. Guiry, DC

PROFESSIONAL ASSISTANTS: COL Robert Todd, DC
LTC Michael Krakow, DC
MAJ Leslie Alexander, VC
Murray Bartley, D.D.S., Univ of Oregon

WORK UNIT NO: 79/86

## TECHNICAL OBJECTIVE

Evaluation of the retained vital root below the crest of the alveolar process to determine if there is any osteogenic activity over the retained root and to evaluate the contents of the pulp tissue to determine if true vitality of the retained root is maintained.

## METHOD

The maxillary right canine tooth will be reduced 5 millimeters below the height of the alveolar bone in 6 one-year-old beagle dogs. A mucoperiosteal flap will be reflected before the tooth is reduced and will undergo primary closure with 5-0 chromic gut. The dogs will be put on a soft diet for 5 days, then changed to normal diets. Healing will be monitored on a weekly basis, visually and radiographically for the first 2 months and then bi-weekly for 8 months. A block of six retained roots will be taken and submitted for histologic evaluation.

## PROGRESS

(79 07 - 79 09) All surgical procedures have been accomplished producing retained roots in six dogs. Healing is complete with no apparent pathology. All dogs are functioning on normal diet. Block sections will be harvested in early January for evaluation.

STATUS: (O)

TITLE: The Effect of Abrasive Polishing Agents on Healing Periodontal Wounds

PRINCIPAL INVESTIGATOR: LTC William B. Hickman, DC

PROFESSIONAL ASSISTANTS: MAJ Lloyd I. Dixon, DC
MAJ Henry Dauber, MC

WORK UNIT NO: 78/27

## TECHNICAL OBJECTIVE

It is widely held true that meticulous professional cleaning of the teeth during the postsurgical phase of periodontal therapy is beneficial to the final surgical result; the use of tooth polishing compounds is a logical extension of this rationale. This project will evaluate the effect of these agents on a standardized periodontal wound in a suitable animal model system. Subcutaneous implant sites will also be done and examined for toxic results.

## METHOD

Young adult Sprague-Dawley laboratory rats will be used in this study in the following manner:

Group I, Week I, 28 rats - the rats will receive, on their prepared backs, subcutaneous implants of the agents to be evaluated. A sham control site will also be placed on the back. Four standard intra-oral wounds will be created, and the same agents implanted, also with a control site. The rats will be sacrificed in groups of two at intervals of 1, 3, 6, 24, 48, 72, and 96 hours, and 5, 7, 9, 11, 14, 21, and 30 days after the operation, for gross and histologic examination. Representative sections of each area will be done by a gross evaluation of the wound healing site and microscopic examination under a high power field observing for neutrophilic infiltrate in the test areas that is in excess to that of the control site. A scoring method of infiltrate per high powered field will be used in order to achieve a quantitative result.

The Effect of Abrasive Polishing Agents - Hickman

Group II, Week II, 28 rats - this group of rats will receive the standard intra-oral wound only with the implantation of the test substances, after which they will receive a standardized typical dental syringe washing of the test areas. A sham control site will be prepared. The animals will be sacrificed, sectioned, and prepared in a manner similar to Group I.

PROGRESS

(78 10 - 79 09) The project has been successfully completed and presented before a professional group. Due to a low population sampling and anesthetic deaths, publication will not be forthcoming.

STATUS: (C)

TITLE: A Comparative Evaluation of the Relative Debriding Efficiency of the Type K and H Files Utilizng 5.25% or 1.00% Sodium Hypochlorite for Irrigation

PRINCIPAL INVESTIGATOR: MAJ W. Richard Liggett, DC

PROFESSIONAL ASSISTANT: COL John W. Harrison, DC

WORK UNIT NO: 76/10

## TECHNICAL OBJECTIVE

The goal of endodontic therapy is to debride and completely obturate the pulp canal system. Since it is the desire of the practitioner to perform his therapy as effectively, efficiently, and with as little threat of toxicity to the patient as possible, the purpose of this study will be twofold. First, to study the relative ability of the Kerr file versus the Hedstrom file in debriding and smoothing the pulp canal wall, and, secondly, to see if there is any significant difference in canal cleanliness when utilizing a 5.25% or 1.00% solution of sodium hypochlorite as pulp canal irrigant.

## METHOD

Forty-eight single-rooted extracted human teeth will be used. These teeth will be frozen as soon as possible following extraction and kept frozen until utilized in the experiment. The 48 teeth will be separated into three groups of 16 teeth, each. One-half of the teeth in each group will be instrumented with a series of Kerr files and the other half with Hedstrom files. Group I will be irrigated with a 5.25 solution of NaOCl; Group II will be irrigated with a 1.00% solution of NaOCl; Group III will be irrigated with saline which will serve as a control. The teeth will then be prepared for histologic examination and evaluation of the debrided and smoothed pulp canal wall.

## PROGRESS

(78 10 - 79 09) This project has been terminated. Technical difficulties resulted in insufficient data to analyze statistically.

STATUS: (T)

TITLE: The Immediate Sealing Properties of Cavit

PRINCIPAL INVESTIGATOR: MAJ Maylon J. Todd, DC

PROFESSIONAL ASSISTANTS: COL John W. Harrison, DC
LTC John P. Heggers, MSC

WORK UNIT NO: 76/09

## TECHNICAL OBJECTIVE

Temporary filling materials are used in endodontics to seal the access cavity between treatments. The purpose of this study is to investigate the immediate sealing ability of Cavit.

## METHOD

Eighteen extracted human teeth were separated into three gourps, each containing six teeth. Access openings were prepared and sealed with Cavit. Group I teeth were immediately immersed in an $S^{35}$ radioisotope solution. Group II teeth were placed in the isotope solution after a five-minute period to allow for maturation of the Cavit restoration. Group III teeth were immersed in the isotope solution after a 15-minute maturation period. After 24 hours in the isotope solution, a central longitudinal section (300 micrometers in thickness) was made from each tooth with a Bronwill thin-sectioning machine. From these central sections, autoradiographs were made and the level of isotope penetration determined.

## PROGRESS

(78 10-79 09) This project is completed and a manuscript has been accepted for publication in the Journal of Endodontics.

Results indicate that the interface between a Cavit temporary restoration and the access cavity wall is a potential pathway for leakage of oral contaminants.

STATUS: (C)

TITLE: The Effect of Root Resection on the Apical Seal

PRINCIPAL INVESTIGATOR: MAJ Maylon J. Todd, DC

PROFESSIONAL ASSISTANT: COL John W. Harrison, DC

WORK UNIT NO: 76/13

## TECHNICAL OBJECTIVE

The purpose of this study is to determine if root resection affects the integrity of the apical seal of previously obturated canals.

## METHOD

Twenty-four extracted single-rooted human teeth were used in this study. Twelve teeth were obturated with gutta percha and sealer, and twelve teeth were obturated with silver points and sealer. Six teeth with each type of obturating material were subjected to the root resection procedure, using a high-speed handpiece and straight-fissure bur. The remaining twelve teeth were not resected and served as controls.

All teeth were placed in a $S^{35}$ radioisotope solution for twenty-four hours. A central longitudinal section was made from each tooth with a Bronwill thin-sectioning machine. From these central sections, autoradiographs were made and the level of isotope penetration determined.

## PROGRESS

(78 10 - 79 09) This project is completed and the manuscript has been accepted for publication in Oral Surgery, Oral Medicine, Oral Pathology, for publication prior to September 1980.

Results indicate that root resection with a rotary instrument in a high speed handpiece does not adversely affect the sealing property of well condensed gutta percha sealer obturations.

STATUS: (C)

TITLE: A Clinical Determination of the Effectiveness of Endodontic Chemomechanical Sterilization

PRINCIPAL INVESTIGATOR: COL David R. Zielke, DC

PROFESSIONAL ASSISTANTS: COL John W. Harrison, DC
LTC John P. Heggers, MSC (Ret)

WORK UNIT NO: 75/22

## TECHNICAL OBJECTIVE

To evaluate the efficacy of an accepted root canal preparation technique in producing sterilization of the root canal system.

## METHOD

The plan is to endodontically treat single-rooted asymptomatic teeth that have roentgenographic evidence of periapical pathosis. All teeth will be isolated with a rubber dam and a conventional access preparation made. Two microbiological samples from each canal system will be made prior to instrumentation and at the completion of instrumentation. One will be incubated in pre-reduced sterilized medium and the other in trypticase soy broth with 0.1% agar as the control. Canal preparation will now be completed in a conventional manner.

At each subsequent appointment, two additional microbiological samples will be obtained before and after instrumentation. All canals will be obturated by the lateral condensation of gutta percha and sealer.

The patients will be reexamined at 6 and 12 month intervals. Another roentgenograph will be made. They will be placed in success or failure categories as defined by Storms. The findings will be correlated with the culture results.

## PROGRESS

(78 10 - 79 09) A total of 244 paired samples were obtained from sixty-one root canal systems at four specific stages of endodontic treatment. Half the samples were placed in a commonly used endodontic medium and incubated aerobically. The remaining samples were placed in PRS medium and incubated in an anaerobic environment. The rereduction procedure, used to remove oxygen entering the PRS medium at the time of insertion of the sample, was not employed. A statistical analysis of the results indicates that the non-rereduced PRS medium is not

as sensitive as rereduced PRS and offers no significant advantages over trypticase soy broth with 0.1 percent agar.

The technical portion of this protocol is completed. Data are being further correlated and work is in progress on an additional publication.

PUBLICATIONS:

Zielke, D.R., Heggers, J.P., and Harrison, J.W.: A Statistical Analysis of Anaerobic vs Aerobic Culturing in Endodontic Therapy. Oral Surg Oral Med Oral Path 42:830-37, 1976.

Zielke, D.R., Heggers, J.P., and Harrison, J.W.: An Analysis of the Sensitivity of Non-Rereduced PRS Medium in Endodontic Therapy. Oral Surg Oral Med Oral Path 47:83-86, 1979.

STATUS: (O)

TITLE: The Relationship of Improving Diabetic Control by Home Monitoring of Blood Glucose to Hemoglobin $A_{IC}$ Measurements and Leukocyte Chemotaxis, Phagocytosis, and Intracellular Killing in Diabetic Patients

PRINCIPAL INVESTIGATOR: CPT Martin Bassett, MC

PROFESSIONAL ASSISTANTS: LTC David McCowen, MC
CPT Martin Crumrine, MSC

WORK UNIT NO: 79/55

## TECHNICAL OBJECTIVE

To demonstrate that chemotaxis, phagocytosis, and intracellular killing by polymorphonuclear leukocytes in diabetic patients can be normalized and maintained by optimum control of blood glucose levels.

## METHOD

Fifteen patients with poor blood glucose control who have had no previous insulin therapy or are poorly controlled on their present regimen and are non-acidotic will be asked to participate. Fifteen healthy volunteers, age matched, without diabetes, cancer, current infection, recent surgery, or having taken any medications for two weeks will be selected to act as controls for the leukocyte function studies.

Blood glucose will be monitored by home use of an Ames "Eyetone" meter and Dextrostix measurements (6 times/day) until stable and then maintaining tight control by weekly measurement of hemoglobin $A_{IC}$. Insulin dosage will be adjusted using twice daily dosages of regular and NPH insulin to closely approximate fasting blood sugars between 80 and 120 mg%.

When the patients are hospitalized for control of their diabetes, they will be instructed in the use of the Dextrostix and the Eyetone meter and in the recording of blood sugar, urine sugar and acetone, caloric intake, and activity, along with instruction in insulin use, diet, etc. A regimen of regular and NPH insulin in the mornings and evenings will be used. Upon return to the home, approximately one week will be needed to "fine tune" the control and stabilize the insulin dosage. Thereafter, when a patient begins to slip from control, he/she will be reissued the home monitoring kit for various periods of time to maintain control.

The Relationship of Improving Diabetic Control - Bassett

Leukocyte Function Tests: Whole heparinized blood will be drawn at the beginning of hospitalization, between 2 and 4 weeks after control, and again 2-4 months after control is achieved, and evaluated along with appropriate control samples.

Hemoglobin $A_{IC}$: Hemoglobin $A_{IC}$ will be checked at the beginning of hospitalization and then weekly during the study with concomitant fasting blood sugars and fasting urine sugar and acetone values to check against the patient's chart of home obtained values and to monitor the overall control over a period of approximately 4-6 months.

PROGRESS

(79 04 - 79 09) The hemoglobin $A_{IC}$ assay technique has been completed, tested, and is on line. Chemotaxis, phagocytosis, and killing assays are being established in control patients. Shortly, patients will be entering the study as glucose meters are on order. Projected completion date is 5-6 months.

STATUS: (O)

TITLE: Study of Daily and/or Diurnal Variation in Angiotensin Converting Enzyme

PRINCIPAL INVESTIGATOR: MAJ Jerome F. Beekman, MC

PROFESSIONAL ASSISTANTS: MAJ Barry J Weled, MC
MAJ Henry D. Covelli, MC

WORK UNIT NO: 79/63

## TECHNICAL OBJECTIVE

To study a group of patients with sarcoidosis and controls to determine whether a daily variation or diurnal variation in serum angiotensin converting enzyme is present.

## METHOD

Ten patients with sarcoidosis and 10 controls (20-50 years of age who do not have any disease known to be associated with elevated angiotensin converting enzymes) will have specimens drawn twice a day, once in the morning and once in the afternoon, for five consecutive days, and the results will be analyzed. An assay for ACE tests will be developed at Clinical Investigation Service and will be used in this project.

## PROGRESS

(79 03 - 79 09) Because of delays in establishing the ability to determine reliable ACE levels at MAMC, this project has not yet been initiated.

STATUS: (O)

TITLE: Diagnostic Utility of CSF Serologies and Rabbit Inoculation in Neurosyphilis

PRINCIPAL INVESTIGATOR: CPT Cornelius P. Brooke, MC

PROFESSIONAL ASSISTANTS: LTC John K. Podgore, MC
CPT Shannon M. Harrison, MC

WORK UNIT NO: 77/93

## TECHNICAL OBJECTIVE

To evaluate the diagnostic utility of cerebrospinal fluid VDRL, FTA, FTA-absorbed, and rabbit testicular inoculation with dark-field microscopic examination in the diagnosis of neurosyphilis.

The second purpose of this project is to determine if adequate cerebrospinal fluid levels of penicillin can be achieved on an outpatient treatment schedule.

## METHOD

Twenty patients will be chosen in whom syphilis of more than one year's duration is suspected. After physical exam, LP will be performed for fluid for animal culture, cell count, glucose, protein, VDRL, and FTA-ABS and FTA-unABS. CSF (0.5 cc) will be injected into the testis of a young male rabbit with a control negative VDRL. Evidence of a positive culture will be taken by darkfield microscopy as demonstration of treponema in the injected testicle and not the control testicle.

One-half of the patients will be randomly selected for treatment with $2.4 \times 10^6$ units benzathine pen IM q. week x 3 as the CDC recommends and retapped 24 hours after the third dose. Penicillin levels will be measured and recorded. If the initial LP was positive for treponema, repeat injection will be carried out with a CSF specimen from three weeks post-treatment.

One-half of the patients will be treated with $1.2 \times 10^6$ units procaine pen IM q. day x 10 days. Repeat LP will be done 4 hours after tenth dose for a measurement of the penicillin levels. If the initial LP was positive for treponema, repeat injection will be carried out with a specimen from three weeks post-treatment.

Diagnostic Utility of CSF Serologies - Brooke

PROGRESS

(78 10-79 09) The principal investigator has been changed to CPT Brooke due to the reassignment of CPT Harrison. CPT Harrison will remain as a professional assistant.

To date, six patients have been studied on the protocol, none of whom have had treponema demonstrated in rabbit passage. More patients will be studied as they become available.

STATUS: (O)

TITLE: Treatment of Rheumatoid Arthritis with Oral Zinc Sulphate

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: COL Robert B. Gibbons, MC
MAJ Michael D. Herring, MC

WORK UNIT NO: 79/12

## TECHNICAL OBJECTIVE

To determine whether changes in serum zinc levels and/or serum histidine levels will correlate with improvements of arthritic symptoms or with occurrence of side effects in patients with rheumatoid arthritis taking oral zinc sulphate.

## METHOD

Patients with rheumatoid arthritis who have been taking oral zinc sulphate will be studied at monthly intervals with evaluation of disease activity accomplished by patient assessment and measurement of grip strength, enumeration of joints with active disease and by sedimentation rate. Blood for zinc and histidine will be drawn at monthly intervals. These subjects will be followed long-term and the investigators will continue to correlate activity of disease with zinc and histidine levels. Statistical analysis of data will compare zinc and histidine with the recorded variables of the disease.

## PROGRESS

(78 11 - 79 09) The values for the serum levels of zinc and histidine were completed the last week of September 1979. Analysis of this data with the clinical data is in progress.

STATUS: (O)

TITLE: Distribution of Gold Used to Treat Rats with Adjuvant Arthritis

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: MAJ George S. Ward, VC

WORK UNIT NO: 79/13

## TECHNICAL OBJECTIVE

To determine the distribution of gold salts injected in rats with adjuvant arthritis and to correlate distribution with effect on the arthritis.

## METHOD

Adult male rats will be given gold by injection or by mouth. Disseminated arthritis will be produced by the injection of Freund's adjuvant. The animals will be sacrificed at 4, 8, 12, and 16 days and tissue surveyed for gold concentration. Clinically, the degree of arthritis will be compared in the control versus the treated animals.

## PROGRESS

(78 11 - 79 09) The preliminary animal work with treatment of rats with adjuvant arthritis with gold has been partially accomplished. The oral preparation of gold has not been supplied by the drug company. It is hoped that supplies will be forthcoming and that the rest of the study can be completed. The analysis of tissues for gold, however, has encountered a technical problem in that the atomic absorption spectrophotometer will not function properly in its present physical setting to the degree of sensitivity necessary in determining the gold tissue concentrations. When this problem is resolved the study can be completed.

STATUS: (O)

TITLE: Distribution of Gold in Tissues of Patients Being Treated with Gold Salts for Arthritis

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: COL Robert B. Gibbons, MC
MAJ Michael D. Herring, MC

WORK UNIT NO; 79/14

## TECHNICAL OBJECTIVE

To measure levels of gold concentration in various tissues in patients being treated with gold for arthritis and to correlate the development of toxicity and response to therapy with these tissue levels.

## METHOD

Subjects will be divided into three groups. Group 1 will be patients receiving gold as current standard treatment who will be studied to establish ranges of gold levels that can occur in tissues during gold therapy. As these patients will not have had objective measurement of disease taken prior to gold, correlation of gold levels and disease will not be possible, but correlation of gold tissue levels with total dose of gold given will be done. Group 2 will be ten patients currently on gold therapy for rheumatoid arthritis. Group 3 will be ten patients not currently on gold but in whom gold therapy is to be started. All patients will continue to receive standard medical treatment.

All groups will have gold levels in lymphocytes, PMN's, RBC's, and urine measured every three months. Gold levels in synovium, lymph nodes, and other tissues will be done on samples acquired at time of any surgery done as part of normal medical care. Clinical studies will be done on Groups 2 and 3. Grip strength, number of affected joints, duration of morning stiffness, and ring size of PIP's will be recorded every three months. Group 3 will have additional gold levels in blood and urine measured at the first and second months. Gold levels will be determined by atomic absorption spectrophotometry. Separation of blood cells will be done by density gradient techniques.

## PROGRESS

(78 11 - 79 09) Tissue samples from patients treated with gold are being collected and frozen for analysis. The analysis of

Distribution of Gold in Tissues of Patients Being Treated with Gold Salts for Arthritis - Cloud

gold levels has encountered a technical problem in that the atomic absorption spectrophotometer will not function properly in its present physical setting to the degree of sensitivity necessary in determining the gold concentrations. When this problem is resolved the study can be completed.

STATUS: (O)

TITLE: I. Determination of the Effects of Chemotherapy and of Malignancy on the Nutritional Status of the Patient; II. Hyperalimentation of Nutritionally Depleted Patients to Improve Their Survival and Response to Chemotherapy

PRINCIPAL INVESTIGATOR: Suresh B. Katakkar, M.D., DAC

PROFESSIONAL ASSISTANTS: LTC Friedrich H. Stutz, MC
LTC Joel W. Black, MC
LTC Charlene P. Holt, MC
MAJ John J. Pelosi, MSC
CPT Jeannie Gallo, SP
Mary J. Oboy, R.N., DAC
Marleen Black, R.N.

WORK UNIT NO: 79/65

## TECHNICAL OBJECTIVE

It has been known that chemotherapeutic drugs by causing nausea, vomiting, and anorexia do interfere with nutrition of cancer patients; however, so does the progressive malignancy. The objective is to measure objectively tumor responses or non-response and the side effects of chemotherapy and do objective measurements of nutritional status of the patients and attempt to delineate what role both chemotherapy and progressive malignancy play in causing nutritional imbalance.

Once inbalance is documented, the investigators plan to hyperaliment these patients and determine the effects on their nutritional status, tolerance of chemotherapy, and objective tumor response.

## METHOD

1. All newly diagnosed cancer patients (approximately 50) will have an assessment of nutritional status as a baseline; including cell mediated immunity.

2. Patients will be classified as having adjuvant chemotherapy or chemotherapy for metastatic disease.

3. Nutritional assessment will be done every 4 weeks and cell mediated immunity will be determined every 12 weeks, unless abnormal at the beginning, on those patients who are on chemotherapy.

4. The side effects at chemotherapy will be graded according to SWOG criteria.

5. The objective response of tumor will be measured every 4 weeks if the objective tumor measurement is by special procedures such as liver or bone scan, in which case they will be done every 12 weeks.

6. If the patient is nutritionally depleted and unable to take oral feeding, then only will he be hospitalized for parenteral feeding or enteral tube feeding. Hyperalimentation will be done for a period of 10-15 days. However, such an aggressive step will be taken only if the underlying malignancy has reasonable chance of response to therapy and meaningful life is judged to be left by the investigators.

## PROGRESS

(79 03 - 79 09) Approximately 25 patients have been entered on the project and entry will be open until January 1980.

STATUS: (O)

TITLE: Dietary Fat and Its Relation to Recurrence of Breast Cancer

PRINCIPAL INVESTIGATOR: Suresh B. Katakkar, M.D., DAC

PROFESSIONAL ASSISTANTS: LTC K. David McCowen, MC
LTC Stephen R. Plymate, MC
LTC Friedrich H. Stutz, MC
MAJ Martin L. Bassett, MC
1LT Ellen Bracy, SP

WORK UNIT NO: 79/66

## TECHNICAL OBJECTIVE

To determine the role of the dietary fat through prolactin-estrogen balance for the recurrence of the breast cancer both in pre and postmenopausal patients.

## METHOD

The plan is to investigate the role of dietary fat by obtaining the normal dietary patterns in high risk group and breast cancer patients (approximately 40). A diet history history will be taken and a blood sample obtained to determine serum prolactin, estradiol, serum cholesterol, and triglyceride levels. These patients will be closely followed in the Oncology Clinic and an attempt will be made to correlate the fat content, prolactin-estrogen ratio, and the recurrence of breast cancer with the disease-free interval.

## PROGRESS

(79 06 - 79 09) One patient has been included in this study. Other patients will be included as they become available.

STATUS: (O)

TITLE: Glucose Homeostasis in Pregnancy and Its Relationship to Gestation and Infant Wellbeing

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
MAJ Jeffery Rakoff, MC
CPT Walter Moore, MC
CPT Charles Saunders, MC
CPT Michael Smith, MSC
William Tuttle, Ph.D., DAC

WORK UNIT NO: 78/37

## TECHNICAL OBJECTIVE

The diagnosis of diabetes has had different criteria during pregnancy. The objective of this study is to identify and analyze the risk factors and mechanisms associated with hyperglycemia and other problems of glucose metabolism during pregnancy.

## METHOD

Retrospective studies will be undertaken. These will be done on clinical data obtained from patients' records, e.g., correlations between blood glucose values, birth weight, outcome of pregnancy, etc. The records utilized will be past records (2 years) available at Madigan Army Medical Center. Patients' involvement will not be required nor will patients be required to undergo any tests. Records will be reviewed by physicians involved and data analyses will be examined by statistical methods. Non-physician assistants will be involved in data analyses only. Identification of risk factors and mechanisms of disease will be analyzed by computer and statistical analysis.

## PROGRESS

(78 10 - 79 09) This project is now near completion. The detailed analyses are being compiled into a manuscript.

Data were analyzed on 52 uneventful pregnancies at risk for diabetes, terminating in physiologic labor and delivery at 40 $\pm$ 2 weeks of the calculated gestation. These data suggest that homeostasis is dynamically related to gestational age even in the absence of diabetes and also that standardization

of populations on the basis of a "normal" glucose tolerance test at undefined weeks of gestation may be questioned. If the magnitude of the fetoplacental unit is responsible for this phenomenon, it is possible that fetal maturation, fetal adiposity, and glycemic indices may have subtle interrelations.

PRESENTATIONS: A Fetal Weight Determinant Based on Maternal Glycemia and Positive Caloric Balance in Non-Diabetic Pregnant Women. Armed Forces District of American College of OB GYN and Armed Forces Seminar (Combined Meeting), 15 Oct 78, Washington, DC.

Maternal Glycemia and Birth Weight - a Spectrum not a Syndrome. Annual Meeting of the American Association for the Advancement of Science, 3 Jan 79, Houston, TX (Abstract #314).

Interrelations of Feto-Placental Maturation, Maternal Glycemic Indices, and Birth Weight. Advanced Postgraduate Course in Hungary, Satellite Symposium to the 10th Congress of the International Diabetes Federation, 16 Sep 79, Budapest, Hungary.

ABSTRACT: Maternal Glycemia and Birth Weight. Abstracts of Endocrinology '79, 7th Biennial International Conference, July 1979, London, England, p 77.

STATUS: (O)

TITLE: Dietary Habits and Birthweights

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
LTC Errol R. Alden, MC
MAJ Charles G. Saunders, MC
CPT Thomas H. Moraczewski, MC
CPT Sarah H. Smith, SP
CPT Michael L. Smith, MSC

WORK UNIT NO: 79/18

## TECHNICAL OBJECTIVE

To examine the dietary habits and their relationship to birth weight in otherwise healthy uncomplicated pregnancies. Preliminary studies suggest that dietary habits are an important variable in studies pertaining to maternal glycemia and the birth weight.

## METHOD

Fifty to one hundred patients with healthy uncomplicated pregnancies will be randomly selected and asked to provide a detailed dietary history. These data in conjunction with information from the patients' charts will be analyzed by statistical methods to reexamine the relationship between dietary habits and birthweight. Women with known risk factors, i.e., high blood pressure, smoking, anemia, weight gain <6 kg or >25 kg, glycosuria, proteinemia, will be excluded from the study.

## PROGRESS

(78 11 - 79 09) Information on dietary habits of subjects during third trimester has been obtained. Investigators are now in the process of obtaining data on fetal outcome.

STATUS: (O)

TITLE: In vitro Studies of Seminal Fluid

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
CPT Martin Crumrine, MSC
CPT Michael Smith, MSC

WORK UNIT NO: 79/67

## TECHNICAL OBJECTIVE

To study the relationship of endocrine indices to male fertility in semen.

## METHOD

Hormonal and biochemical indices will be measured in seminal fluid samples collected from approximately 40 patients undergoing vasectomy or attending the Infertility Clinic. A routine semen analysis will be done, including pH. The following parameters will be measured: FSH, LH, prolactin, testosterone, dihydrotestosterone, fructose, and citric acid. In addition, binding studies will be performed on spermatozoa to determine the various roles of these components in fertility. A follow-up will be done on these patients using the medical record as the source.

## PROGRESS

(79 03 - 79 09) The gathering of semen samples is still in progress. A number of samples thus far collected do not lend themselves to statistical analysis; therefore, a larger number of samples must be collected.

STATUS: (O)

TITLE: Adrenocortical Reserve in Patients with Metastatic Carcinoma

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
LTC Friedrich H. Stutz, MC

WORK UNIT NO: 76/05

## TECHNICAL OBJECTIVE

To evaluate the adrenocortical reserve in patients with metastatic carcinoma by alpha 1-24 ACTH stimulation.

## METHOD

Patients with documented metastatic carcinoma (lungs, bone, etc.) will be tested with alpha 1-24 ACTH (Cortrosyn$^{R}$) according to common clinical procedures after baseline serum cortisol levels have been obtained. In those patients demonstrating a suboptimal adrenal reserve, repeat stimulation will be performed after chemotherapy has been given to detect improvement in the reserve function of the adrenal gland.

## PROGRESS

(78 10 - 79 09) No change in adrenocortical function has been detected in those patients evaluated and the protocol has been terminated.

STATUS: (T)

TITLE: The Role of Thyroid Suppression in the Treatment of Thyroid Cysts

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANT: COL Bruce L. Fariss, MC

WORK UNIT NO: 76/18

## TECHNICAL OBJECTIVE

To evaluate the efficacy of thyroid suppression in the treatment of benign thyroid cysts.

## METHOD

All patients with suspected thyroid nodules will be referred to the Thyroid Clinic where evaluation of the nodule with palpation, radionuclide scanning, and ultrasonography will be performed. Blood studies to include $T_3$RAIU, $T_4$CPB, serum $T_3$, and thyroid antibodies will be done. Those patients with cystic lesions as shown by these studies will undergo percutaneous needle aspiration of the cysts, and the aspirated fluid will be evaluated with cytological examination.

Patients with successful aspirations will be referred to a disinterested party for randomization. If the patient's random number is even, he will be started on an equivalent of three grains of desiccated thyroid hormone. If the random number is odd, he will be started on an identical placebo. The patients will be followed for a minimum of one year. A minimum of 20 patients will be utilized for the study.

## PROGRESS

(78 10 - 79 09) Twenty patients with benign thyroid cysts were studied in a prospective double-blind fashion to determine the effect of thyroid suppression on the recurrence of these cysts after aspiration. When the ten patients receiving placebo medication were compared with the ten patients ingesting thyroid hormone, no significant difference in the time either group was free of cyst recurrence was found. The investigators conclude that thyroid suppression is not effective in the prevention of benign thyroid cyst recurrence after initial aspiration. This work has been accepted for publication in the American Journal of Medicine.

STATUS: (C)

TITLE: The Effect of Aspirin on Blood and Urine Thyroxine in Induced Primate Hyperthyroidism

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ George S. Ward, VC

WORK UNIT NO: 77/03

## TECHNICAL OBJECTIVE

To evaluate the effect of aspirin on the fate of serum and urine thyroxine in pigtail macaque monkeys.

## METHOD

Eight *Macaca nemestrina* monkeys were paired and given 1.0 mg $LT_4$ intravenously 24 hours before receiving 1.2 mg ASA, orally, on the morning of the study. One monkey received the ASA with the other receiving only $LT_4$. Baseline serum $T_4$ levels were drawn and repeated at 30 minute intervals during the period 2 to 4½ hours after the ASA was given. Urine $T_4$ levels were determined at 30 minutes intervals, 2 to 4½ hours after the ASA was given, and serum ASA levels were determined at 3 hours after administration. Six weeks later, the same pair of monkeys were studied in identical fashion, with the exception that control monkeys received the ASA with the other monkey serving as the control. $T_4$ levels were determined by RIA in the Clinical Investigation Laboratory.

## PROGRESS

(78 10 - 79 09) The animal model utilized was changed from the canine to the primate because the thyroid system of the monkey more closely parallels that of the human. Thus the title was changed from "canine hyperthyroidism" to "primate hyperthyroidism." The experimental phase has been completed and clinical material is presently being examined. Initial results have thus far failed to establish any effect of salicylates on excretion and/or metabolism of thyroid hormone.

STATUS: (O)

TITLE: Comparison of the Protein-Sparing Modified Fast with Conventional Dietary Therapy in the Treatment of Obesity

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: COL James W. Reed, MC
MAJ Wijdan A. Luqman, MC
MAJ Edward Przasnyski, MC
CPT Robert B. Chadband, MC
CPT Nancy Cronmiller, AMSC
CPT Raymond Parker, MSC
CPT Sarah Smith, AMSC

WORK UNIT NO: 78/07

## TECHNICAL OBJECTIVE

This protocol will explore the efficacy of treating obese patients with an outpatient experimental diet as compared with conventional diet therapy as currently administered by Diet Therapy at MAMC. This study will address the initial rate of weight loss, the success of chronic therapy in maintaining the achieved lower weight, the problem of loss of muscle (protein) mass resulting in fatigue and poor compliance, and the psychological variables in individuals being treated for obesity to seek ways of psychological intervention which might increase the effectiveness of the diet regime.

## METHOD

Adult obese patients 30% above ideal body weight (IBW) will be identified and referred for evaluation. A complete physical examination and a biochemical screen will then be done. Patients will be randomly assigned to either the Protein-Sparing Modified Fast (PSMF) (1.5 gm/kg/IBW/day lean protein plus prenatal vitamins, one/day; Titralac tablets 2 bid; K-lyte one/day) or a conventional 1000 calorie diet. The patients will be seen by the contact physician every month for a follow-up SMAC-20 and reassessment. Five standard psychological assessment procedures will be given before the beginning of diet therapy, after weight reduction to approximately 50% of IBW, when IBW is reached, approximately three months after reaching IBW. Upon achievement of IBW, the patients will be entered on maintenance programs and followed for a period of 9 months.

Comparison of the Protein-Sparing Modified Fast with Conventional Dietary Therapy in the Treatment of Obesity - McCowen

PROGRESS

(78 10 - 79 09) The technical portion of this project has been completed, and the data are presently being reviewed. Early analysis establishes the efficacy of the PSMF diet in short term, but not chronic, treatment of simple obesity.

STATUS: (O)

TITLE: Association of Hypercalcemia, Hypertension, and the Use of Thiazide Diuretics

PRINCIPAL INVESTIGATOR: MAJ Edward J. Przasnyski, MC

PROFESSIONAL ASSISTANTS: LTC David McCowen, MC
MAJ Marjorie McGinnis, ANC

WORK UNIT NO: 78/33

## TECHNICAL OBJECTIVE

To perform a retrospective analysis of a group of hypertensive patients in order to discover the incidence of hypercalcemia, whether it is reversible, and if it is associated with the use of thiazide diuretics.

## METHOD

A large group of hypertensive patients seen by the nurse clinician in the hypertensive clinic over the past eight months (approximately 1500) will have their charts reviewed to determine the incidence of hypercalcemia, association of the hypercalcemia with medications (notably thiazide diuretics), and to arrange follow-up to determine the etiology of the hypercalcemia.

Patients with hypercalcemia on two occasions within the past year will be evaluated in the Endocrine Clinic if the hypercalcemia persists after discontinuing thiazides for one month.

## PROGRESS

(78 10 - 79 09) Data complilation is complete, and data are being analyzed. The charts of 651 patients were reviewed for thiazide use and calcium levels. Those who had had at least one calcium level greater than 10.5 mg% in the past 12 months were asked to have repeat calcium levels performed. Of these, 13.7% (85 patients) had a calcium greater than 10.5 mg%. These patients were told to discontinue thiazides and had repeat calcium 60 to 90 days later. Thirty-three patients were consistently hypercalcemic and were thoroughly evaluated and followed over a period of 4 to 12 months. The following summarizes findings in this group: parathyroid adenoma, 3 patients; multiple

myeloma, 1 patient; persistent hypercalcemia (no etiology found), 1 patient; slow resolution of hypercalcemia; 25 patients; lost to follow-up, 3 patients. The range of time to resolution was 4 to 18 months (mean 6.7 months).

Additionally, 235 patients had had calcium determinations prior to any thiazides (at time of diagnosis of hypertension). Of these, 111 had had elevated calciums in the last 12 months, 124 had not. The mean pre-thiazide calcium in the former group was 10.04 mg%, and the latter, 9.68 mg%. There were 27 patients who had never been on thiazides and their mean calcium was 9.73 mg%. The mean calcium for the entire group (624 patients) on thiazides was 10.29 mg%.

STATUS: (C)

TITLE: Gonadotropin Responses to Gonadotrophic Releasing Hormone as Predictor of Fertility in Oligospermic Males Treated with Clomiphene Citrate

PRINCIPAL INVESTIGATOR: MAJ Edward J. Przasnyski, MC

PROFESSIONAL ASSISTANTS: MAJ Jeffery S. Rakoff, MC
LTC K. David McCowen, MC
COL James W. Reed, MC

WORK UNIT NO: 78/50

## TECHNICAL OBJECTIVE

To determine whether gonadotropin responses in men with oligospermia before or during treatment with clomiphene citrate will predict those who will eventually respond with increased fertility.

## METHOD

Fifteen to twenty-five males who meet the following criteria will be entered into the protocol: (1) three sperm counts $<15 \times 10^6$ with three days abstinence prior to sample collection; (2) good general health, on no medications, and evidence of normal sexual function present; (3) wives have been carefully evaluated and are normal or fertility problems corrected; (4) normal serum testosterone, prolactin, and LH levels; and (5) normal FSH level.

Normal FSH level will be determined from three pooled samples collected at 30 minute intervals. Three FSH, LH levels will be drawn at 15 minute intervals and then patients will be given a baseline GNRH bolus. FSH, LH will then be drawn at 15, 30, 45, 60, 90, 120, and 180 minutes after the bolus. The patients will then be started on clomiphene citrate, 25 mg daily for 25/30 days, for a minimum of six months. GNRH testing will be completed as described above during the second and fourth months of therapy. The patients will have monthly sperm analyses, and serum testosterone, LH, and FSH levels will be drawn monthly. Patients will be continued on clomiphene citrate up to 12 months if a response (increased counts by 25-50%) is demonstrated in the first six months. A patient will be dropped from the study group at six months if no response to clomiphene is seen or if the wife becomes pregnant.

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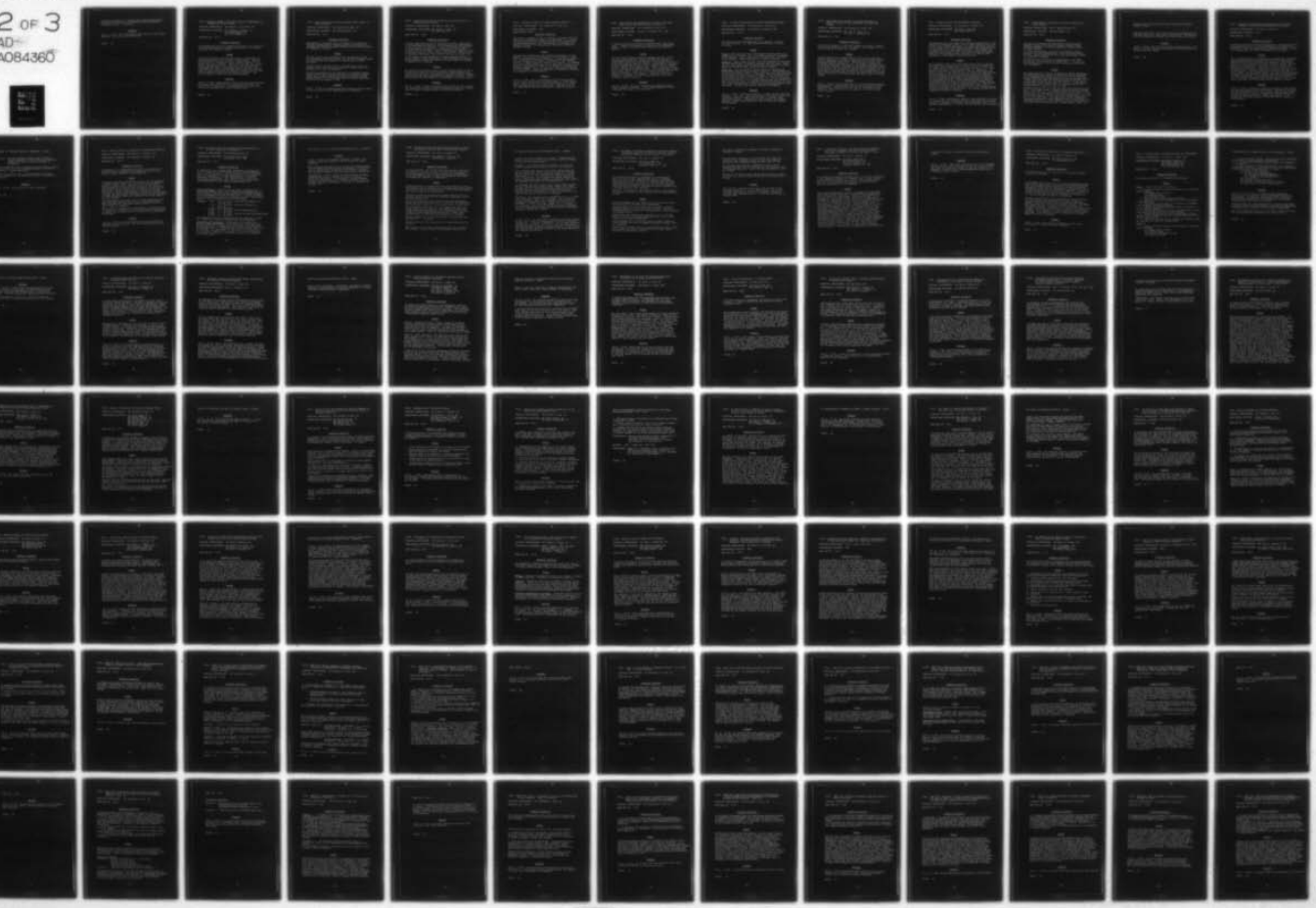

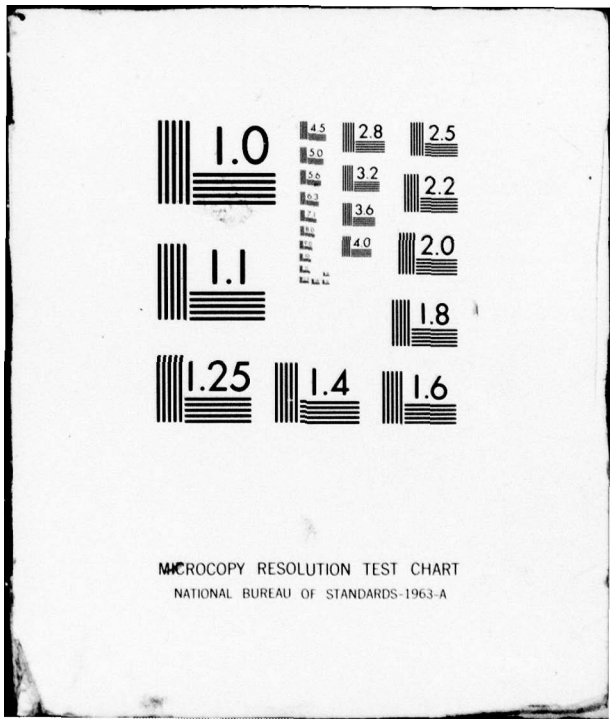


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Gonadotropin Responses to Gonadotrophic Releasing Hormone as Predictor of Fertility in Oligospermic Males Treated with Clomiphene Citrate - Przasnyski

PROGRESS

(78 10 - 79 09) The investigators were unable to obtain GNRH. Therefore, the protocol was terminated.

STATUS: (T)

TITLE: Hormonal Changes in Patients Placed on Cimetidine for Treatment of Ulcer Disease

PRINCIPAL INVESTIGATOR: MAJ Edward J. Przasnyski, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
MAJ David McCowen, MC
CPT Verle Bohman, MC

WORK UNIT NO: 79/70

## TECHNICAL OBJECTIVE

To determine the effect of Cimetidine therapy on the levels of various polypeptide and steroidal hormones prior to, during, and after this therapy in adults.

## METHOD

Thirty male patients who have been placed on Cimetidine for therapeutic reasons will be asked to participate. Histories will be taken to include fertility, ethanol intake, use of medications, and illnesses. Basal levels of FSH, LH, testosterone, dihydrotestosterone, estradiol, and prolactin will be determined from serum. The patient will be asked to have blood drawn for these determinations again two weeks and four weeks following initiation of Cimetidine therapy and two weeks and four weeks following discontinuance of therapy. Sex steroid globulin levels will also be determined.

## PROGRESS

(79 06 - 79 09) Approximately ten patients have been evaluated with blood drawn before and at varying intervals after the institution of Cimetidine. The investigators are now in the process of performing the various hormonal RIA's.

STATUS: (O)

TITLE: Serum Angiotensin Converting Enzyme (ACE) Levels in Thyroid Disease

PRINCIPAL INVESTIGATOR: MAJ Edward Przasnyski, MC

PROFESSIONAL ASSISTANT: CPT Martin Bassett, MC

WORK UNIT NO: 79/71

## TECHNICAL OBJECTIVE

Measurement of serum ACE levels in patients with hyperthyroidism, hypothyroidism, euthyroid goiter, and controls to determine the interrelationship between ACE and these diseases as compared to controls.

## METHOD

Patients seen by the investigators in the Endocrine Clinic for evaluation of thyroid disease will have blood samples drawn for thyroid function studies as a routine part of their evaluation.

Controls will be patients seen in the Endocrine Clinic for problems other than thyroid who will have samples drawn as a routine part of their evaluations.

Statistical analysis will be undertaken to determine whether patients with thyroid dysfunction have statistically higher levels than a control group consisting of patients without thyroid disease or other diseases known to elevate ACE levels by the use of an unparied t test.

## PROGRESS

(79 03 - 79 09) All samples have been collected and are being evaluated for ACE levels (approximately 50 patients).

STATUS: (O)

TITLE: Cooperative Study for the Analysis of Risk Factors in Young Coronary Patients

PRINCIPAL INVESTIGATOR: COL James W. Reed, MC

PROFESSIONAL ASSISTANTS: COL Everett Cooper, MC
COL John Haas, MC

WORK UNIT NO: 72/06

## TECHNICAL OBJECTIVE

A unique opportunity exists in the Army to study a large group of young coronary patients by pooling together the case material of all the Class II hospitals. It is the purpose of this study to investigate these patients in comparison to age-matched controls for the following: obesity, hypertension, family history of coronary disease, plasma lipid classification, smoking history, carbohydrate intolerance, and insulin response to glucose load.

In the study of these parameters in young coronary patients, those factors of major importance in the development of coronary disease should be detected because they have caused the disease to manifest at a young age.

## METHOD

All patients who develop proven coronary disease under the age of 40 who are patients at any of the Class II Army hospitals are subjects for the study. Age-matched individuals without coronary disease from the same institution will serve as controls. Patients and controls will be studied for the parameters as listed above.

## PROGRESS

(78 10 - 79 09) Twenty-two patients were studied on this project. The conclusions are that a better indication of risk for coronary artery disease in young patients is the LDL cholesterol.

STATUS: (C)

TITLE: Daunomycin Therapy in Acute Leukemia (Phase II)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/04

## TECHNICAL OBJECTIVE

This is not a research study, but rather a treatment protocol involving an experimental drug. The objective is to continue the use of daunomycin in combination with other conventional chemotherapeutic agents for the treatment of leukemia as an extension of Phase I of the protocol, but with a different regimen of drugs.

## METHOD

Daunomycin in combination with cytosine arabinoside, 6-thioguanine, vincristine, and prednisone will be given for seven days as remission induction treatment. A bone marrow sample will be obtained in 2-4 weeks; if evidence of the leukemia persists, a second induction course will be given. If leukemia cells are visibly absent, one to two additional courses will be given as consolidation therapy in an attempt to eliminate any residual leukemic cells. At that point, maintenance therapy will be provided. Dosage and duration of therapy are outlined in paragraph 6.0 of the protocol.

## PROGRESS

(78 10 - 79 09) Due to the departure of LTC Irving Pierce, the principal investigator has been changed to LTC Friedrich Stutz. During FY 79, one patient was treated on this study with complete remission for 18+ months. Previous to FY 79, one other patient had been treated with complete remission.

STATUS: (O)

TITLE: Case Control Questionnaire for Patients with Large Bowel Cancer and Their Relatives Without It.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/78

## TECHNICAL OBJECTIVE

To identify and confirm factors associated with large bowel cancer. Controls are siblings of patients with large bowel cancer in order to eliminate most hereditary and cultural factors.

## METHOD

All colo-rectal cancer patients at Madigan who are, in the opinion of the physician, willing and able to complete a questionnaire and have a sibling who is willing and able to do the same will be asked to complete a questionnaire including questions regarding life style, diet, family history, medical history, and the Srole Anomie Scale. Phase I will be a pilot study to include 30-50 matched pairs. After evaluation of the pilot study, Phase II will be initiated to include 500+ matched pairs of patients. There will be an annual follow-up of patients and analysis of response. Long-term follow-up is planned to determine if risk factors correlate with actual colorectal cancer incidence.

## PROGRESS

(79 08 - 79 09) The pilot study has been completed and is being evaluated at present. A final questionnaire is being formulated for Phase II of the project.

STATUS: (O)

TITLE: In vitro Identification of Tumor Associated Antigens

PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC

PROFESSIONAL ASSISTANT: CPT Martin H. Crumrine, MSC

WORK UNIT NO: 75/14

## TECHNICAL OBJECTIVE

The purpose of this investigation is to identify, using an in vitro technique, the tumor associated antigens of breast carcinoma.

## METHOD

Phase I: Ten $C_3H$-strain mice with implanted murine breast carcinoma will be obtained, and, after tumor growth has progressed beyond palpable stage, the mice will be sacrificed, and tumor tissue removed. Tissue treatment as listed in protocol.

Phase II: Tumor tissue obtained from the Department of Pathology (either from autopsy or surgical specimen) and non-tumor tissue from the same subject will be emulsified and treated in a similar manner as the mouse tumor tissue outlined in Phase I.

Phase III: Once the specific tumor associated antigens from mouse breast carcinoma are separated (Phase I), the antigens will be pooled and held at -80°C. Forty $C_3H$-strain mice with implanted murine breast carcinoma will be obtained. Ten of these mice will be separated and have no further procedures. Twenty other mice will undergo resection of the tumor mass, and ten will subsequently receive an injection of the specific murine tumor associated antigens (obtained in Phase I) combined with Fruend adjuvant, followed by a booster injection with tumor associated antigen without tumor resection. The mice will then be observed and compared.

## PROGRESS

(78 10 - 79 09) Insufficient amounts of tumor material have been produced in the mice. When approximately 30-40 gms of tumor are available, further attempts will be made to identify tumor associated antigens. Progress has been limited since smaller amounts of tumor yielded equivocal results from the columned chromatography.

STATUS: (O)

TITLE: Serum RAST Titer Changes in Allergic Patients on Desensitization and the Correlation with Skin Test Changes

PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC

PROFESSIONAL ASSISTANTS: LTC Joel W. Black, MC
LTC John C. Espinosa, MC

WORK UNIT NO: 77/67

## TECHNICAL OBJECTIVE

To study the changes in serum IgE reagenic antibody at various times during desensitization and compare these changes with the clinical course and skin test results.

## METHOD

Patients seen by the Allergy Service will be given the usual allergy evaluation to include clinical history, physical examination, appropriate skin tests, laboratory blood tests, and pulmonary function spirometry. A 5 cc aliquot of serum will be reserved and tested for specific IgE reagenic antibody titers by the RAST technique, performed by the Nuclear Medicine Service. Those patients who are placed on densitization treatment will be reevaluated at appropriate intervals by the Allergy Service, at which time serum will again be drawn for repeat RAST titers and compared with skin test results and correlated with the clinical course.

## PROGRESS

(78 10 - 79 09) Initial RAST titers to various pollens obtained. Approximately 10 patients have been placed on desensitization immunotherapy. Repeat RAST titers will be repeated at yearly intervals. More patients will be added to the study as they become available.

STATUS: (O)

TITLE: Immunotherapy of Murine Mammary Carcinoma

PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC

PROFESSIONAL ASSISTANTS: LTC Joel W. Black MC
MAJ George Ward, VC

WORK UNIT NO: 77/77

## TECHNICAL OBJECTIVE

Immunotherapy has as yet made only a minimal contribution to the treatment of malignant disease, due in large measure to the lack of pure tumor associated antigen. If tumor associated antigen were obtained in pure form and administered with Levamisol so as to enhance the anti-tumor immune response, after surgery and chemotherapy had reduced tumor load, results might be markedly improved. The purpose of this protocol is to explore that possibility, using mammary tumor-bearing mice.

## METHOD

Murine mammary tumors from tumor-bearing mice will be excised, the tumor tissue homogenized in saline and freeze-thawed, and the supernatant concentrated by dialysis against dry silica gel and passed through G-200 sephadex column for separation. The separate fractions so obtained will then be concentrated and small aliquots of each fraction will be tested for tumor antigen by skin testing on the mice whose tumors have been excised. Fractions identified as having tumor associated antigens will then be processed by quantitative electrophoresis to separate the individual proteins. These individual fractions will be concentrated and the fraction containing tumor antigen will be identified by skin testing on tumor-excised mice. After identification of specific tumor antigen fractions, more will be separated from additional tumor and used to treat various groups of mice as outlined in the protocol. All groups of mice will be compared for length of survival.

## PROGRESS

(78 10 - 79 09) Insufficient tumor has been available to utilize as antigen and until sufficient tumor is available, this project can not be completed. Anticipate that sufficient tumor will be available approximately 1 Jan 80, and this project can be completed.

STATUS: (O)

TITLE: Dysrhythmias in Patients with Chronic Obstructive Airway Disease

PRINCIPAL INVESTIGATOR: MAJ W. Douglas Weaver, MC

PROFESSIONAL ASSISTANT: Leonard Hudson, M.D.

WORK UNIT NO: 79/10

## TECHNICAL OBJECTIVE

To study the incidence and importance of dysrhythmias in ambulatory chronic obstructive pulmonary disease (COPD) patients compared to a control population without cardiopulmonary disease.

To study the influence of severity of pulmonary disease, arterial blood gas abnormalities, serum electrolyte abnormalities, serum theophylline levels and serum digoxic levels on dysrhythmia incidence.

To evaluate the association of dysrhythmias in the COPD patient with the occurrence of sudden death. The value of dysrhythmia detection in predicting subsequent sudden death will be examined.

## METHOD

The study group will consist of ambulatory adults fulfilling the American Thoracic Society criteria for chronic bronchitis and/or emphysema with $FEV_{1.0}/VC$ of less than 1.64 times the standard deviation from the predicted ratio and absolute $FEV_{1.0}$ of less than 1.64 times the standard deviation from the predicted value (based on sex, age, and height). An age and sex matched group with no known heart or lung disease has been studied and will serve as a control group.

Patients selected for the study will have the following on the day of Holter monitoring: pulmonary function tests to include $FEV_{1.0}$, FVC, $FEF_{25-75}$, and resting arterial blood gases in the seated position; resting ECG; serum electrolytes (Na, K, Cl, $CO_2$) and calcium; complete blood count; serum theophylline level just prior to the next dose if the patient is on any theophylline containing preparation; serum digoxin level if the patient is receiving digitalis; 24-hour ambulatory cardiac monitoring with an Avionics Electrocardiorecorder, single-channel, Model 400,

with precordial MCL-1 chest lead, with diary recording of all symptoms, activities, and times of medications. The subjects will be encouraged to perform their usual routine activities.

## PROGRESS

(79 01 - 79 09) This protocol has been terminated due to the departure of the Principal Investigator and the inability to receive technical support.

STATUS: (T)

TITLE: The Work of Breathing on Continuous Positive Airway Pressure versus Positive End-Expiratory Pressure

PRINCIPAL INVESTIGATOR: MAJ Barry J Weled, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/40

## TECHNICAL OBJECTIVE

To evaluate the work of breathing involved in continuous positive airway pressure versus positive end-expiratory pressure and to determine if there is a significant difference in oxygen consumption between these two modes of mechanical ventilation.

## METHOD

Ten to twenty patients with hypoxemia on a mechanical ventilator requiring end-expiratory pressure will have flow and pressure monitors which do not interfere with mechanical ventilation inserted in the mechanical ventilator delivery system. Measurements will be made while the patient is on five minutes of positive airway pressure. Two trials (order of trials will be randomized) of each mode of pressurizing ventilation will be run on each patient. The flow sensor will integrate the flow to tidal volume, and the pressure sensor will record airway pressure. A respiratory integrator will combine flow and volume and obtain the work of breathing. An oxygen analyzer will be placed in line, and oxygen consumption will be calculated for the various trials utilizing the volume measurements referred to above.

## PROGRESS

(78 10 - 79 09) A duplicate study was reported in Chest before the necessary equipment was operational. Therefore, the project has been terminated. Out of this project came an appreciation of the relation of airway to intraplueral pressures and a new concept was generated which is under investigation at the University of Florida College of Medicine with Dr. Weled as a coinvestigator.

STATUS: (T)

TITLE: Management of Premature Rupture of Membrane (PROM) in Patients at 36 Weeks (+) Gestation

PRINCIPAL INVESTIGATOR: CPT Kevin C. Kelley, MC

PROFESSIONAL ASSISTANT: COL Joseph Sakakini, MC

WORK UNIT NO: 78/26

## TECHNICAL OBJECTIVE

To assess fetal and maternal outcome in patients with premature rupture of membranes.

## METHOD

To determine the best management in patients with PROM utilizing either pitocin augmentation/induction or expectant management, the subjects will be randomly assigned to one of the following groups:

Group A:
1. Speculum exam to establish PROM.
2. Endocervical C&S aerobic by sterile speculum
3. OB exam - Leopold to establish position and vaginal to establish station, dilation, effacement, and Bishop score.
4. Prep
5. Enema
6. Hourly temperatures
7. Pitocin augmentation/induction
8. External and internal monitoring as indicated
9. Delivery by OB criteria

GROUP B: #'s 1, 2, 3, 4, 6, and 9 the same as Group A
5. enema only after clinical criteria for labor established by 5 min contractions x $1^{o}$ on external monitor accompanied by pain, nausea, vomiting, need to push, bloody show/or further bloody show.
7. pitocin augmentation only after definite evidence of hypotonic uterine inertia in active phase at Cx C/5.
8. external monitoring only until other criteria for active phase established.

Management of Premature Rupture of Membranes - Kelley

Group C: The same as Group B except that no digital vaginal examination will be done until definite evidence of labor by clinical criteria is established.

Rupture of membranes will be assessed by gross vaginal pooling of fluid per os or by both nitrazene positive and positive examination of vaginal secretions.

Duration of gestation will be assessed based on history, physical examination, and laboratory results as outlined in the protocol.

PROGRESS

(78 10 - 79 09) This protocol has been terminated.

STATUS: (T)

TITLE: Hormonal Assay As a Predictor of Spontaneous Abortion

PRINCIPAL INVESTIGATOR: CPT Michael S. Phillips, MC

PROFESSIONAL ASSISTANT: LTC Stephen R. Plymate, MC

WORK UNIT NO: 79/76

## TECHNICAL OBJECTIVE

To determine if, by measurement of one or a combination of hormones early in pregnancy, spontaneous abortion in the first or second trimester can be predicted.

## METHOD

Two groups of patients (50 patients each) will be studied in a similar manner. Blood will be drawn for determination of prolactin, progesterone, estradiol, HCG, and sex steroid binding globulin at the initial visit and at two week intervals through the fourteenth week of pregnancy (12th week of gestation). Control patients will be solicited through inclusion of request with pregnancy kits and will be limited to those that are no more than eight weeks from the last menses at their evaluation (making a minimum of four blood samples for each patient).

The second group of patients will be those presenting at no more than eight weeks gestation as a threatened abortion. These patients will have blood samples drawn at 8, 10, 12, and 14 weeks of pregnancy.

Results will be analyzed both individually as predictors and in combination, hopefully to discover one assay or combination of assays that is 100% accurate in prediction of spontaneous miscarriage.

## PROGRESS

(79 09 - 79 09) No work has been done on this protocol as approval was received only a few days before the end of the reporting period.

STATUS: (O)

TITLE: The Effect of In Vivo Vitamin B6 Supplementation on In Vitro Lymphocyte Transformation

PRINCIPAL INVESTIGATOR: CPT Richard Keniston, MC

PROFESSIONAL ASSISTANTS: CPT Michael Smith, MSC
Louis Matej, M.T., DAC

WORK UNIT NO: 79/21

## TECHNICAL OBJECTIVE

To demonstrate that optimum human lymphocyte transformation in vitro requires in vivo vitamin B6 (as pyridoxal phosphate, PLP). PLP is required for the biosynthesis of the polyamines, which are required for optimal DNA synthesis by nitrogen-stimulated T-lymphocytes. Most human beings are far from being saturated with PLP, and, therefore, their immune function might benefit from vitamin B6 supplementation.

## METHOD

Normal volunteers: Ten male and ten female volunteers will follow the schedule below. All lymphocyte transformations (LT) will be done by the $^{3}$H-thymidin uptake method without mitogen, using phytohemagglutinin and concanavalin A. Vitamin B6 assays will be completed on serum by an enzymatic method. Total blood drawn for both procedures will be 20 ml/drawing.

Schedule:
- 0 wks - L.T., B6 assay, begin multivitamines, p.o. 2 mg B6, q.d.
- 4 wks - L.T., B6 assay, begin B6 vitamins p.o., 50 mg q.d.
- 6 wks - L.T., B6 assay
- 12 wks - L.T., B6 assay, end B6 supplementation
- 14 wks - L.T., B6 assay
- 20 wks - L.T., B6 assay, end multivitamin supplementation
- 24 wks - L.T., B6 assay

The magnitude of mitogen stimulation will be compared in steps 1-7. These will also be correlated with serum B6 levels.

Chronically ill volunteers: Chronically ill patients with apparent immune deficiency will be identified. B6 levels will be determined and the immune dificient patients will be given B6 supplementation. A condensed form of the schedule above will be followed. Any improvement in the patient's in vitro and in vivo immune response will be noted. In vitro response will be measured by lymphocyte transformation and in vivo response by clinical signs.

The Effect of In Vivo Vitamin B6 Supplementation - Keniston

PROGRESS

(79 01 - 79 09) All necessary equipment, reagents, and vitamins have been acquired, and PLP assays are being perfected.

Urine reagents obtained for this project have demonstrated that the aminoglycoside antibiotics Kanamycin and Gentamicin and the antimicrobial Primaquine form covalent complexes with pyridoxal phosphate and could thus deplete vitamin B6.

PRESENTATION: Role of Vitamin B6 and Putrescine in Human Lymphocyte Activation: Beneficial Effect of Dietary Vitamin B6 Supplements. Joint Meeting, British Columbia Society of Clinical Chemists and American Association for Clinical Chemists (NW Section), 20-22 Sep 79, Harrison Hot Springs, BC.

STATUS: (O)

TITLE: The Role of Bacterial and Chlamydial Agents in Acute Epididymitis and the Effect of Antibiotic Therapy

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: CPT Robert U. Finnerty, MC
COL Alfred S. Buck, MC

WORK UNIT NO: 78/20

## TECHNICAL OBJECTIVE

To determine what role certain infectious agents (*Mycoplasma, Neisseria gonorrhoeae, Chlamydia trachomatis,* and aerobic colliform bacteria) play in the etiology and pathogenesis of acute epididymitis; and to compare two commonly used forms of therapy for treatment of epididymitis.

## METHOD

Study population: All males seen with the diagnosis of acute epididymitis who are hospitalized at Madigan Army Medical Center and who have had no antibiotic therapy in the month preceding the current episode of epididymitis.

Controls: A group of age and race-matched controls will be selected from Ft Lewis military personnel undergoing routine physical examinations.

Two urethral swabs will be obtained using calcium alginate swabs; the first for culture of *N. gonorrhoeae* and Gram stain; the second for culture of *C. trachomatis* and *U. urealyticum*.

Urine specimens: The first 10 cc of voided urine and a midstream urine will be obtained. The sediment of the first voided urine and midstream urine will be examined for number of WBC per high-powered field and bacteria. Both urine specimens will be cultured quantitatively for coliforms.

Blood specimens: 10 cc will be obtained by venipuncture for serology for *C. trachomatis*.

Similar urine and blood specimens will be obtained from the controls.

When surgery is clinically indicated to rule out torsion of the testicle, direct cultures of epididymal fluid will be

obtained at scrotal exploratory surgery. Radionucleatide scrotal scans will be done on all patients within 48 hours to rule out testicular torsion.

Treatment: All patients will be placed at bed rest with scrotal elevation until afebrile and pain has subsided.

If no coliforms are seen on the initial unspun urine and the midstream urine culture shows less than $10^3$ coliforms per ml, the patient will be randomly treated with 100 mg doxycycline b.i.d. for 10 days or with 500 mg ampicillin q.i.d. for 10 days. If the patient's medical records or history indicate possible allergy to either of these agents, the alternate safe agent will be administered.

If coliforms are seen on the initial unspun urine or grown from any specimen with colony counts greater than $10^3$/ml, patients will be treated individually according to results of urine cultures and antibiotic sensitivity patterns. Patients will be instructed not to have intercourse for at least 14 days after initiation of treatment.

Follow-up: All patients will be reexamined at 3, 7, 14 days, and 6 weeks after initiation of therapy. The presence of scrotal erythema, edema, and tenderness will be noted and recorded by standard protocol. Repeat cultures will be performed at 7 and 14 days and 6 weeks for *C. trachomatis*, *U. urealyticum*, and any other pathogen initially recovered. Ten cc of convalescent blood will be obtained for serologic testing at 14 days and 6 weeks.

## PROGRESS

(78 10 - 79 09) At this time, 19 patients have been included in the study. Eight of nineteen have culture or serologic evidence of *C. trachomatis* infection. Two of eight have been treated with ampicillin, and six of eight with doxycycline. The investigators continue to enroll patients, but no correlation will be done until the procedures have been completed on all subjects and controls.

STATUS: (O)

TITLE: The Effect of Antibiotic Therapy in the Last Trimester of Pregnancy Upon the Incidence of Neonatal Conjunctivitis and Pneumonia Due to *Chlamydia trachomatis*.

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ Richard Belts, MC
Catherine Yokan, M.D., DAC

WORK UNIT NO: 78/38

## TECHNICAL OBJECTIVE

To determine the effect of treatment with erythromycin, 500 q.i.d. for 14 days, administered orally to pregnant women during the last trimester of pregnancy with cervical *Chlamydia trachomatis* colonization. The incidence of subsequent neonatal colonization and conjunctival and pulmonary infection will be noted in treatment and control infants over a one-year interval after delivery.

Addendum: The effect of erythromycin therapy on the vaginal and neonatal carriage of this organism will be simultaneously studied.

## METHOD

Cervical specimens will be obtained on sterile cotton swabs during the routine 32-week pelvic examination.

Serum specimens will be obtained from a portion of blood routinely drawn for rubella antibody screening. The microimmunofluorescent serology for chlamydia will be done according to standard methods.

Conjunctival and nasopharyngeal specimens will be obtained during the nursery discharge examination and at the 4 week, 2 month, and 6 month examinations.

Serum specimens will be obtained from the study children at 6 and 12 months for the microimmunofluorescent serology titer for chlamydia.

Conjunctival specimens will be obtained from all study infants that present with acute conjunctivitis for Giemsa stains, bacterial and chlamydial cultures.

The Effect of Antibiotic Therapy in the Last Trimester of Pregnancy - Podgore

Nasopharyngeal specimens will be obtained for Gram stain, bacterial, and chlamydial culture in all study infants presenting with pneumonia during the first year of life.

All patients with positive chlamydial cultures will be assigned randomly into the treatment and non-treatment groups. The treatment group will receive 500 mg erythromycin q.i.d. for 14 days.

Culture of the vaginal vault and rectum for Group B streptococci prior to and following therapy with erythromycin will be done.

PROGRESS

(78 10-79 09) Sixteen patients have been entered in the treatment group and 20 in the control group. The infants are being followed for evidence of chlamydial infection. A control and treatment group of 50 each are anticipated by February 1980.

STATUS: (O)

TITLE: A Survey of *Chlamydia trachomatis* Cervical Colonization in Late Pregnancy and Conjunctival and Naso-Pharyngeal Carriage in the First Six Months of Life

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ Richard Belts, MC
CPT Larry Mellick, MC
Catherine Yokan, M.D., DAC

WORK UNIT NO: 78/41

## TECHNICAL OBJECTIVE

To determine the baseline carriage rate of *Chlamydia trachomatis* in the endocervix during late pregnancy and its relationship to various factors including age, parity, socio-economic status, race, and the development of subsequent post-partum fever, neonatal conjunctivitis, and pneumonia.

## METHOD

The study population will consist of pregnant military dependents seen at MAMC during the 35 week gestation examination and all infants of these women. Cervical specimens will be obtained on sterile cotton swabs during the 35 week pelvic examination, immediately placed into carrying medium and stored at -70°C and transported to the isolation laboratory at the University of Washington weekly. Serum specimens will be obtained from a portion of blood routinely drawn at this time. Microimmunofluorescent serology for chlamydia will be done according to standard methods. Conjunctival specimens and naso-pharyngeal specimens will be obtained at the nursery discharge examination and at 4 weeks, 2 months, and 6 months. Conjunctival specimens for Giemsa stain and bacterial and chlamydial cultures will be obtained from all study infants that present with acute conjunctivitis as will naso-pharyngeal specimens for Gram stain. Bacterial and chlamydial cultures will be obtained from all study infants that present with pneumonia during the first year of life. Serum will be obtained from all study infants at six months to measure serum antibody to chlamydia by microimmunofluorescent methods.

A Survey of *Chlamydia trachomatis* Cervical Colonization - Podgore

PROGRESS

(78 10 - 79 09) This study will continue until 50 treatment and 50 control patients are selected for the study involving the effect of antibiotic therapy in the last trimester of pregnancy. Results of 365 cultured patients reveals an 11% colonization rate (40/365).

STATUS: (O)

TITLE: The Role of *Campylobacter* in Pediatric Enteritis

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: CPT Martin Crumrine, MSC
CPT Larry Mellick, MC

WORK UNIT NO: 79/09

## TECHNICAL OBJECTIVE

To determine the role of *Campylobacter* in acute diarrheal disease of childhood.

## METHOD

To determine the role of *C. fetus* in acute diarrhea of childhood, rectal swabs taken from a group of children presenting with acute diarrhea will be placed in selective medium and atmospheric conditions for campylobacter organisms as well as routine bacterial studies for enteric organisms. A group of children presenting for problems other than diarrhea will be selected as matched controls to determine the carriage of *C. fetus* in the general pediatric population.

Patients presenting with acute diarrhea and control patients will have rectal swabs obtained and placed in Stuart's transport medium and then plated on selective campylobacter medium in less than 6 hours for overnight culture. The selective medium consists of blood agar with the addition of Vancomycin (10 mg/L), polymyxin B (2.5 IU/ml), and trimethoprim (5 mg/L). These plates will then be incubated at 43°C in an atmosphere of 5% oxygen, 10% carbon dioxide and 85% hydrogen overnight. The swabs will also be processed in the usual manner for enteric organisms.

## PROGRESS

(79 02 - 79 09) The study will commence as soon as the investigators are able to obtain the media.

STATUS: (O)

TITLE: Cryopreservation of Human Platelets for Transfusion

PRINCIPAL INVESTIGATOR: CPT Dennis E. Urban, MSC

PROFESSIONAL ASSISTANTS: MAJ Robert Ridgway, VC
MAJ Robert Usry, MSC
MAJ Joseph Yetter, MC
CPT Kris Shekitka, MC

WORK UNIT NO: 77/06

## TECHNICAL OBJECTIVE

To preserve platelets for transfusion by freezing.

## METHOD

Phase I. Freeze and recover platelets.

a. Screen 10 healthy routine blood donors of O positive blood including:
(1) normal donor criteria
(2) platelet count
(3) salicylate level

b. Draw one unit of blood from each donor.

c. Red cells and other components to be used routinely by the Blood Bank.

d. Preparation of platelets for freezing in accordance with the Dayian and Rowe procedure.

e. Aliquot each prepared platelet pack to be used as control and for testing.

f. Thaw platelets after 36 hours by submersion in a 40°C water bath with mild agitation for 20 seconds.

g. Sample control and test for bacteriologic control. Culture by the automated bacterial detection method on blood agar and peptone broth.

h. Test both test and control samples for platelet count and osmolality of platelet concentration.

Phase II.

a. Screen 20 healthy routine blood donors of O positive blood including:
(1) normal donor criteria
(2) platelet count
(3) partial thromboplastin time
(4) salicylate level

b. Draw one unit of blood. Red cells and other components minus PRP to be used routinely by blood bank.

c. Preparation of platelets for freezing (see paragraphs e-h, Phase I).

d. Test platelets, frozen and nonfrozen, for viability of recovered platelets in accordance with criteria established by Dayain and Rowe (Cryobiology 13:1-8, 1976).

(1) uptake of $^{14}C$ serotonin
(2) (a) ADP induced aggregation
    (b) epinephrine induced aggregation
    (c) collagen induced aggregation
(3) clot reaction
(4) response to hypotonic shock
(5) platelet recovery and size distribution
(6) osmolality of platelet concentration

PROGRESS

(78 10 - 79 09) In vitro testing has been temporarily halted due to the departure of key individuals and shortage of personnel. Testing will resume when blood collection bags with ACD anticoagulant are received and new personnel become familiar with testing procedures.

An article entitled "Cryopreservation of Platelets Simplified: A Modified Glycerol-Glucose Method" concerning the preliminary testing has been accepted for publication by Transfusion.

Due to the departure of MAJ Usry, CPT Dennis Urban has assumed the role of principal investigator on this protocol.

STATUS: (O)

TITLE: Rejuvenation of Outdated Human Erythrocytes and Evaluation of Frozen Blood Techniques

PRINCIPAL INVESTIGATOR: CPT Dennis Urban, MSC

PROFESSIONAL ASSISTANTS: CDR C. Robert Valeri, MC, USNR
LTC Marshall E. Hinckley, MC
MAJ William J. Hunter, MC
CPT Kris Shekitka, MC
Dolores LaBarge, MT, DAC

WORK UNIT NO: 77/45

## TECHNICAL OBJECTIVE

To determine the safety and efficacy of human red cells stored at $4^{o}C$ for 22-28 days that are biochemically modified (rejuvenated) prior to freeze-preservation; and to evaluate two techniques to freeze and deglycerolize human erythrocytes for utilization at Madigan Army Medical Center.

## METHOD

Phase I: Rejuvenate and refreeze 30 units outdated O-positive or O-negative red cells and ship to the Naval Blood Research Laboratory, Boston, MA, for complete freeze-thaw-wash recoveries on the red cells, bacterial cultures, and measurement of the red cell 2, 3-DPG, ATP, and potassium ion levels in addition to in vitro $P_{50}$ levels. Red cell survival measurements will be performed on selected units.

Phase II: Rejuvenate and refreeze 30 units of expired blood, the same as Phase I with the exception of the removal of the supernatant solution containing glycerol, the solution used for biochemical modification, and plasma that is present in the concentrated red cells prior to freezing. These units will be shipped and evaluated as in Phase I.

Phase III: Same procedures as in Phase II with the exception that freezing will be accomplished in the original blood bag and shipped as in Phase I and II.

Rejuvenation of Outdated Human Erythrocytes - Urban

PROGRESS

(78 10 - 79 09) 2,3 DPG levels were performed on 20 units of red cells prior to freezing or rejuvenation/freezing. Post-thaw testing has been delayed due to a shortage of personnel. In-vitro testing will continue whenever possible.

Due to the departure of MAJ Usry, CPT Dennis Urban has assumed the role of principal investigator on this protocol.

STATUS: (O)

TITLE: A Teaching Model for Pediatric Intubation Utilizing Ketamine-Sedated Kittens

PRINCIPAL INVESTIGATOR: LTC Errol R. Alden, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ Ronald W. Brenz, MC

WORK UNIT NO: 74/19

## TECHNICAL OBJECTIVE

To teach infant resuscitation procedures to nurses, nurse clinicians, OB-GYN residents, and other nonpediatric physicians who may be called upon to treat pediatric emergencies. Many physicians and paramedics have never had the training opportunity to attempt intubation of an awake living creature. The kitten, immobilized with ketamine hydrochloride, gives the student the opportunity to visualize vocal cords, precipitate laryngospasm, and learn the difficulties associated with emergency intubation.

## METHOD

Weaned kittens, weighing 0.5 to 1.0 kg will be used in these teaching sessions. Ketamine hydrochloride (22 mg/kg) plus atropine sulfate (0.04 mg/kg) will be administered intramuscularly to each kitten. Intubation will be performed with the kittens on their backs, using a pediatric laryngoscope, and sizes 8-14 French endotracheal tubes. Kittens may be used for several consecutive weekly sessions until they grow too large to be utilized. The procedure is not harmful to the kittens.

## PROGRESS

(78 10 - 79 09) The teaching model was incorporated into a scientific exhibit, entitled "Teaching Models for Neonatal Resuscitation" which has received several awards at national meetings in prior years. It has also been responsible for numerous clinics, the latest at the District NAACOG Meeting where 50 individuals utilized this model. The investigators have been invited to organize a clinic for the Seminar on Pediatric Intensive Care in April 1980. The project continues to be utilized at MAMC as a teaching model.

STATUS: (O)

TITLE: Ambulatory Adolescent Health Care Needs: Implications for Pediatric Training Programs

PRINCIPAL INVESTIGATOR: LTC Errol R. Alden, MC

PROFESSIONAL ASSISTANTS: Peter E. Johnsen, M.D.

WORK UNIT NO: 78/39

## TECHNICAL OBJECTIVE

To determine from collated data of all Adolescent Clinic visits for one year (1) the common health care needs of this population of adolescents; (2) where the focus of teaching effort should be in training residents; and (3) in which areas useful research could be entertained. This study will also serve as a quality control function for the Adolescent Clinic.

## METHOD

For one calendar year, assign each new patient a file card, including name, SSN, year of birth, sex, race, sponsor's rank, and status. For each patient visit, the physician will write the diagnoses of the problems encountered on that visit on the file card to be coded by the clinic staff. At the end of the year, the following data will be tabulated: (1) number of patients/patient visits; (2) number of patients/patient visits for each diagnostic category; and (3) demographic data: sex, year of birth, race, sponsor's rank and status. The collated data will then be evaluated for those areas in which resident education would be beneficial and a curriculum derived.

## PROGRESS

(78 10 - 79 09) Due to the departure of Dr. Johnsen, LTC Alden has assumed the role of principal investigator on this protocol. The work has been accomplised and the data accumulated. A manuscript is in preparation. The study supports the impression of adolescent specialists that pediatricians with adolescent patients would benefit from training in the areas of normal adolescent growth and development (physical and psychological), interviewing skills, facility in managing psychosocial and psychosomatic problems, and skills in the management of the obstetric/gynecologic

needs of this population. In addition, the need for specific training in the recognition and optimal management of common orthopedic problems should be emphasized.

STATUS: (O)

TITLE: Clinical Trials of a Peripheral Capillary Blood Culture Sampling Technique

PRINCIPAL INVESTIGATOR: LTC Errol R. Alden, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
LTC Robert Modarelli, MC
LTC John P. Heggers, MSC
MAJ Richard P. Knudson, MC
CPT John R. Hofmann, VC

WORK UNIT NO: 76/28

## TECHNICAL OBJECTIVE

To compare the effectiveness of a new peripheral capillary blood culture sampling technique with standard blood culture methods in human neonatal and adult patients. This technique has been demonstrated effective in three animal species and needs clinical trials to determine whether it may be used as a supplemental sampling method in man.

## METHOD

Group I - Neonatal Patients - Infants suspected of having transient bacteremia or frank sepsis will be sampled for blood culture in the usual manner. In addition, peripheral capillary blood will be sampled at the same time via heel stick, and the results will be compared to those achieved by the standard method. Blood for pour plates will also be drawn.

Group II - Adult Patients - The capillary blood culture technique (finger stick) consists of meticulous skin preparation and drawing of 0.1 - 0.2 ml of blood into a heparinized tuberculin syringe with 20 gauge needle attached. The needle is changed and the blood is injected into a standard blood culture bottle. Results are read at 24 and 48 hours and subcultures are performed where necessary. Routine blood culture will also be performed in each case.

A population of adult patients undergoing urological instrumentation in the Urology Service will be sampled before their procedure and at 5, 15, and 30 minutes following the procedure, comparing standard blood culture technique and the capillary blood culture sampling technique. Patients undergoing transurethral resection of the prostate, urethral dilation, prostatic

Clinical Trials of a Peripheral Capillary Blood Culture Sampling Technique - Alden

biopsy, cystoscopy, and other urological manipulations are felt to have a relatively high incidence of bacteremia.

## PROGRESS

(78 10 - 79 09) LTC Alden has assumed the role of principal investigator on this protocol due to the departure of MAJ Knudson. This project has been completed and a paper has been accepted for publication in Pediatrics.

A new micro heelstick blood culture technique was evaluated in 40 neonates who were clinically felt to be septic. Heelstick cultures were positive in 11 and peripheral venous cultures were positive in 8. All 8 venous cultures had positive heelstick cultures. Heelstick blood cultures seem to be at least as sensitive as venous cultures.

STATUS: (C)

TITLE: Development of an Assay for Methylphenidate and Ritalinic Acid in Human Plasma and Urine

PRINCIPAL INVESTIGATOR: CPT Allen L. Neese, MC

PROFESSIONAL ASSISTANT: CPT Michael L. Smith, MSC

WORK UNIT NO: 79/61

## TECHNICAL OBJECTIVE

To develop two assays for methylphenidate and ritalinic acid in human plasma and urine. A radioimmunoassay for both compounds will be developed and compared to a gas-chromatography technique similar to those reported in the medical literature.

## METHOD

For this assay, a gas-liquid chromatogarph with flame ionization detector will be used. The sample of plasma or urine will be acidified and extracted with an organic solvent. Alkalinization with sodium tetraborate and subsequent organic extraction will separate methylphenidate and ritalinic acid. The organic phase will be used to assay methylphenidate and the aqueous phase will be acidified, evaporated, derivatized, and extracted with organic solvent to assay for ritalinic acid. In addition, methylphenidate will be coupled to methylated bovine serum albumin using a carbodiimide synthesis. This conjugate will be injected into rabbits and the resulting antibody used to develop a radioimmunoassay for methylphenidate and ritalinic acid. Samples used in both analyses will be excess plasma or urine samples from other clinical investigators to which known amounts of each compound have been added.

## PROGRESS

(79 03 - 79 09) Quotations for contract services from four laboratories for either HPLC assays or RIA assays have been unrewarding. The principal investigator has requested that the protocol be terminated due to the decreased availability or technical support and an increased patient load placed upon himself.

STATUS: (T)

TITLE: Tension Pneumothorax - A Teaching Model

PRINCIPAL INVESTIGATOR: MAJ Amil Ortiz, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ George S. Ward, VC

WORK UNIT NO: 76/29

## TECHNICAL OBJECTIVE

To provide training in diagnostic and surgical skills in the treatment of tension pneumothorax and to provide ongoing teaching sessions.

## METHOD

New Zealand white rabbits weighing 700-2500 grams are anesthetized initially with an intramuscular injection of ketamine hydrochloride and promazine hydrochloride. Five minutes after injection, the chest wall is shaved and prepared for surgery. EKG leads are placed on the rabbit and the heart rate and QRS voltage monitored on an oscilloscope. Surgical procedure as outlined in protocol. During the training session, the pathophysiology of TPT is discussed with each student. The entire training session can be accomplished in less than two hours for a group of 3 to 5 people.

## PROGRESS

(79 07 - 79 09) Three groups of approximately ten people each, consisting of medical students, nurses, and medical personnel have attended these teaching sessions since this protocol was reactivated in July. This program will be ongoing with plans for ICU students and new interns and residents to attend these sessions as well as pediatric personnel in order that all involved in this procedure may have training in the actual technique on a regular basis.

STATUS: (O)

TITLE: The Neonatal Cardiac Index, A Valuable Prognosticator of Neonatal Well-Being

PRINCIPAL INVESTIGATOR: MAJ Amil Ortiz, MC

PROFESSIONAL ASSISTANTS: MAJ Bernard R. Hannam, MC
MAJ Lawrence K. Wickham, MC
SP/4 Bret A. Hargrave

WORK UNIT NO: 79/68

## TECHNICAL OBJECTIVE

The Neonatal Cardiac Index (NCI) during the first 24 hours of life, together with the APGAR scores can serve as a valuable tool in predicting the outcome of neonatal life. Patterns of heart rate during this period ot time reflect the ability of the newborn myocardium to react to endogenous stimuli of catecholamines as well as exogenous stresses and developmental factors. The investigators propose to study this parameter in the premature infant of different gestational ages.

## METHOD

A total of 100 premature newborns will be separated in groups of 25 according to gestational age (28-30 weeks, 30-32 weeks; etc.). All infants will have cardiorespiratory monitoring in the first 5 minutes of life, at 1, 12, and 24 hours of age. A Corometrics 512 neonatal monitor will be utilized as it is the only monitor with the capability of assessing beat to beat variations in heart rate. Upon delivery of the infant, a sample of 0.5 cc of heparinized blood will be taken from the placental side of the umbilical cord for the purpose of blood gas determination. The neonatal cardiac index and variability patterns will be determined in each monitoring period. A correlation of the NCI with the APGAR scores, blood pH, and gestational age will be made as well as the outcome of the infant.

## PROGRESS

(79 03 - 79 09) To date, 34 reactivity records have been obtained of premature infants. More infants will be studied before analysis of data commences.

STATUS: (O)

TITLE: Standardization of a Screening Instrument for Developmental Soft Signs in Normal Children

PRINCIPAL INVESTIGATOR: LTC Carl A. Plonsky, MC

PROFESSIONAL ASSISTANT: CPT Heather Smith, MC

WORK UNIT NO: 79/16

## TECHNICAL OBJECTIVE

To devise and standardize a screening examination for neuro-developmental soft signs. Standardization will be done on a large number of normal children. The examination will then be given to a number of children with known minimal brain dysfunction and the results compared.

## METHOD

A soft signs screening examination, method manual, and score sheet have been devised. The screening examination will be individually administered to 100 normal children, grades kindergarten through third grade. Thirty children will be tested by more than one examiner on the same day as a test for inter-examiner reliability, and 30 children will be re-tested one week later as a test of test-retest reliability. The age at which each of the developmental signs is found to be absent in 90% of this normal population will be calculated and tabulated. A sample of children with known MBD will be given the examination and the results compared to those of the normal population. After the pilot study is completed, the test instrument will be evaluated and refined and given to the entire on-post school population, kindergarten through third grade.

## PROGRESS

(79 02 - 79 09) The technical portion of this protocol is complete. The results are being analyzed and refined and presentation is anticipated at the American Academy of Pediatrics Meeting in October 1979. Also, preparation of a manuscript has begun.

STATUS: (O)

TITLE: A Prospective Analysis of the Current Pediatric Screening Program (PSP) to Critically Evaluate Its Effectiveness and Application to Other Military Pediatric Clinics

PRINCIPAL INVESTIGATOR: Carl E. Stracener, M.D., DAC (COL, Ret)

PROFESSIONAL ASSISTANT: LTC James Nelson, MC

WORK UNIT NO: 77/44

## TECHNICAL OBJECTIVE

To determine through a comprehensive data analysis the effectiveness of the PSP to identify and treat pediatric patients who prior to its conception had not been receiving comprehensive, organized health care past the first year of life. In addition, this project will detail the PSP organization, methodology, and availability of application to other military clinics using the paraprofessional services of local Red Cross volunteers.

## METHOD

A prospective study of 500 routine screenings was conducted including information concerning early detection of vision, speech and hearing deficiencies, deviant physical and psychomotor development, dental disease, high blood pressure, anemia, bacteriuria, significant family history and environmental influences, immunization lags, and potential learning disabilities. The statistics were analyzed to document the need and effectiveness of the PSP. An analysis of the follow-up treatment necessary for those individuals identified with abnormalities was conducted.

## PROGRESS

(78 10 - 79 09) Five hundred children were studied to determine characteristics of the population served, quality of the work of the volunteers and the number of new problems identified. Use of well-trained volunteers, provided with adequate supervision and follow-up physical examination of the children, identified many new problems at minimal cost and proved an effective means of expanding quality health care.

A Prospective Analysis of the Current Pediatric Screening Program - Stracener

In conjunction with assisting other military hospitals in program implementation, a video tape of a representative family and medical history intake and routine screening appointment was completed.

PUBLICATION: Child Health Assessment and Screening Using a Volunteer Staff. Nelson, J.H., Stracener, C.E., and Gannon, C. Western Journal of Medicine 129:243-49, 1978.

STATUS: (C)

TITLE: Maintenance of Patency of the Ductus Arteriosus in Congenital Cardiac Lesions. (Upjohn Cardiovascular Diseases Research Protocol #2907 - Multi-Clinic)

PRINCIPAL INVESTIGATOR: MAJ Warren H. Toews, MC

PROFESSIONAL ASSISTANT: LTC Errol Alden, MC

WORK UNIT NO: 78/44

## TECHNICAL OBJECTIVE

To examine infants with cyanotic congenital heart diseases to see if the patency of the ductus can be maintained by infusion of Prostaglandin $E_1$. The minimal effective dose and side effects of this agent will be determined.

## METHOD

This study is being done as a group study with Upjohn. In infants in whom blood is flowing through the ductus from the aorta to the pulmonary artery, a catheter will be placed through the umbilical artery to the first part of the descending aorta, at or just above its junction with the ductus. Prostaglandin $E_1$ will be infused continually into this region at the rate of 0.1 mcg/kg/min until the desired ductal effect is achieved, and then the dose will be decreased to 0.05 mcg/kg/min. In infants in whom blood flow is passing through the ductus from the pulmonary artery to the aorta, a catheter will be placed in the pulmonary artery proximal to the ductus arteriosus and Prostaglandin $E_1$ will be infused at the rate of 0.1 mcg/kg/min until the desired ductal effect is achieved, and then the dose will be decreased to 0.05 mcg/kg/min. Further dose adjustments in either case will be made, but doses greater than 0.1 mcg/kg/min will be documented as to reason. In the event that the major artery cannot be catheterized, the infusion will be given into a large vein. The infusion will be continued until surgery can be performed, usually a matter of hours. An angiogram will be performed before and after infusion as will serum creatinine, liver function studies, blood glucose, Ca, CBC, and urinalysis. Blood pressure, arterial blood gases, pH, temperature, pulse rate, respiratory rate, and general condition will be monitored hourly. Evidence of increased femoral pulses, decreased acidosis, increased urine output, or improvement of congestive heart failure will be noted. The investigator will monitor

any changes in clinical condition and note an opinion as to its possible relationship to the drug.

In decreased pulmonary blood flow, evidence of efficacy will be evaluated in the following ways: (1) increase of $pO_2$; (2) evidence of the patency of the ductus at surgery or at autopsy; (3) confirmation of ductal dilation with $PGE_1$ by angiograms.

In interrupted aortic arch, evidence of efficacy will be evaluated in the following ways: (1) a decrease in the gradient in pressure between the pulmonary artery and the aorta; (2) increased femoral pulses; (3) decreased acidosis; (4) increased urine output; (5) improvement in congestive heart failure; (6) confirmation of ductal dilation with $PGE_1$ by angiograms.

## PROGRESS

(78 10 - 79 09) This protocol has been terminated at MAMC due to the departure of the principal investigator. Three patients were studied at MAMC and the results forwarded to Upjohn to be incorporated in the group analysis.

STATUS: (T)

TITLE: Quantitation of Intracardiac Shunts in Experimental Animals by Radionuclide Angiocardiography (RAC)

PRINCIPAL INVESTIGATOR: MAJ Warren H. Toews, MC

PROFESSIONAL ASSISTANTS: MAJ George S. Ward, VC
CPT Steven G. Wynder, MC
William K. Tuttle, Ph.D., DAC

WORK UNIT NO: 79/19

## TECHNICAL OBJECTIVE

The hypothesis exists that quantitation of intracardiac left-to-right (L-R) and right-to-left (R-L) shunts by RAC is more accurate than oximetry utilizing the Fick principle - especially for shunts at the atrial level. The purpose of this project is to verify this hypothesis in the experimental animal.

## METHOD

Twenty adult mongrel dogs will be placed on a mechanical ventilator under general anesthesia. A thoracotomy will be performed and a length of polyethylene tubing will be placed connecting the left and right atrial appendages. Blood flow rate will be controlled at a constant level sufficient to vary the pulmonary-to-systemic flow ratio between 1:1 and 2.5:1 or greater. Electromagnetic flow probes will be placed around the ascending aorta and the main pulmonary artery. Catheters will be placed in the aorta, left pulmonary vein, pulmonary artery, and superior and inferior vena cava for blood sampling for oximetry. Several determinations of L-R and one of R-L shunts will be performed by RAC with simultaneous determination of shunt by oximetry and electromagnetic flow.

## PROGRESS

(78 11 - 79 09) This project has been terminated due to the departure of the principal investigator.

STATUS: (T)

TITLE: Effects of Simulated Altitudes in Pregnant Sheep

PRINCIPAL INVESTIGATOR: MAJ Lawrence Wickham, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ Bernard Hannam, MC
MAJ Richard Knudson, MC
MAJ Amil Ortiz, MC
MAJ Warren Toews, MC
MAJ George Ward, VC
SP/4 Bret Hargrave

WORK UNIT NO: 79/73

## TECHNICAL OBJECTIVE

To observe the physiologic changes in pregnant sheep subjected to simulated altitudes and the effects Terbutaline has on these changes, i.e., maternal arterial and venous oxygen content and pressure. A followup study is planned to assess the effects of simulated altitude changes on maternal uterine blood flow and fetal physiologic changes. Upon completion of the two part project, the investigators anticipate making recommendations concerning ante partum maternal air transport medical care.

## METHOD

Four pregnant sheep will have a spinal anesthetic and halothane administered by face mask until endotracheal intubation can be accomplished. Catheters will be placed in the carotid and jugular vessels for monitoring and continuous blood gas sampling.

The animal will be placed on a respirator at a predetermined minute ventilation. The oxygen concentration will be changed by using an analyzed gas mixture. Levels of 15, 12, and 9% oxygen will be maintained until stabilization of blood gases occurs and the percentage corresponding to the level of oxygen available in a pressurized airplane flying at normal heights will be maintained for 2 hours.

Maternal arterial and wedge pressures will be monitored. Maternal cardiac output will be determined and maternal and fetal heart rate will be monitored.

The effects of Terbutaline on the altitude-induced physiologic changes will be studied using an electromagnetic flow probe on the uterine artery and invasive fetal monitoring.

Effects of Simulated Altitudes in Pregnant Sheep - Wickham

PROGRESS

(79 03 - 79 09) This protocol has been terminated. A report has recently been published in the medical literature on the results of similar studies.

STATUS: (T)

TITLE: Serum Cortisol and Incidence of Hyaline Membrane in Premature Sheep Pretreated with Steroids: Single vs Multiple Gestations

PRINCIPAL INVESTIGATOR: MAJ Lawrence Wickham, MC

PROFESSIONAL ASSISTANTS: MAJ Bernard Hannam, MC
MAJ Amil Ortiz, MC
MAJ George Ward, VC
CPT Michael Byrne, MC

WORK UNIT NO: 79/81

## TECHNICAL OBJECTIVE

To attempt to show increased incidence HMD in multiple gestation pregnancies, even if pretreated with steroids; then to treat a second group of multiple gestation sheep with an increased dose of steroids and compare rates of HMD Group 1 to Group 2.

## METHOD

Three groups of 4 sheep will be studied: Group A - single fetus; Group B - two or more feti; Group C - two or more feti. Groups A and B will be given a standard dose of steroid at less than 135 days gestation and Group C will be given twice the standard dose of steroids.

Amniocentesis will be performed at 24 and 48 hr post-steroid injection for L/S ratio determination.

At delivery - approximately 72 hrs after steroids - maternal and fetal cortisol levels will be drawn. A maternal cortisol will have been determined before any experimental manipulation.

Newborn gastric aspirate or tracheal aspirate L/S ratios will be obtained.

Lambs will be watched for respiratory distress syndrome. Lung tissue will be obtained for pathologic diagnosis of hyaline membrane disease from all neonatal mortalities or up to 50% of the survivors will be sacrificed to obtain this tissue.

## PROGRESS

(79 07 - 79 09) Sheep have been purchased and are presently being "time-mated" for more exact gestational age determination. Normal plasma cortisols will be determined in pregnant sheep in Jan 80.

STATUS: (O)

TITLE: Implantation of Intraocular Lenses

PRINCIPAL INVESTIGATOR: LTC Stanley C. Allison, MC

PROFESSIONAL ASSISTANTS: COL Stanley C. Sollie, MC
LTC Christopher G. Knight, MC
MAJ Bruce E. Bellin, MC
CPT Lawrence E. Hannon, MC

WORK UNIT NO: 79/64

## TECHNICAL OBJECTIVE

To become proficient in intraocular lens implantation and to gain investigator status with FDA requirements, thereby providing a new technique in ophthalmic surgical care for our patients.

## METHOD

1. Obtain appropriate instruments to accomplish the procedure.
2. Obtain research investigator status with companies that have FDA approval to supply the lenses.
3. Implant lenses in 10 rabbits as a training experience for surgical nurses and assistants in this procedure.
4. Implant lenses in appropriately selected patients in order to provide visual rehabilitation.
5. To eventually establish this as a routine procedure in the military medical armamentarium of ophthalmic care.

## PROGRESS

(79 07 - 79 09) Investigators are in the process of certification through the individual suppliers for the use of the lenses. The training phase will begin when the lenses are obtained.

STATUS: (O)

TITLE: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint

PRINCIPAL INVESTIGATOR: LTC Richard A. Camp, MC

PROFESSIONAL ASSISTANTS: MAJ Ernest Miller, MC
MAJ Robert Weatherwax, MC

WORK UNIT NO: 79/53

## TECHNICAL OBJECTIVE

To document that instability resulting from injury to the radial collateral ligament causes significant disability and to emphasize the frequency of this injury which to this time has been reported as uncommon or rare.

## METHOD

1. Documentation of the frequency of this injury versus the reportedly much more common ulnar collateral ligament injury. For this purpose, all operative cases of surgical repair or reconstruction of ulnar and radial collateral ligament injury or instability for the previous two-year period will be reviewed.

2. Clinical evaluation of the presenting symptom complex of these patients with radial collateral ligament instability.

3. Clinical evaluation of results of a surgical procedure modified for use by the investigators for radial collateral ligament instability which has been reported for use in ulnar collateral ligament instability by Nevaiser, et al, J Bone Joint Surg, Oct 71. This evaluation will include pre- and post-operative range of motion and amount of instability to stress testing.

## PROGRESS

(78 12 - 79 09) This study is complete. From the study, the investigators concluded the following:

1. Significant injury to the radial collateral ligament of the thumb metacarpophalangeal joint is more common than previously realized.

Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint - Camp

2. The acute injury is frequently not diagnosed and is often inadequately treated.

3. Chronic radial instability results in a symptom complex that is distinct from that of ulnar instability.

4. Ligament reconstruction and dynamic repair using the abductor pollicis brevis proved to be a reliable method of treatment for symptomatic chronic instability of the radial collateral ligament of the thumb metacarpophalangeal joint.

PRESENTATION: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint. American Society for Surgery of the Hand, San Franciaco, CA, 18-23 Feb 79.

ABSTRACT: IBID: J Hand Surg 4:286, 1979

PUBLICATION: Camp, R.A., Weatherwax, M.C., and Miller, E.B.: Chronic Post-Traumatic Radial Instability of the Thumb Metacarpophalangeal Joint. Accepted for publication, J Hand Surgery.

STATUS: (C)

TITLE: An Investigation to Compare the Effect of Renal Function of Conservative versus Surgical Management of Blunt Renal Trauma in Canines

PRINCIPAL INVESTIGATOR: CPT Carl F. Cricco, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ George E. Brannen, MC
CPT Jonathan S. Vordermark, MC

WORK UNIT NO: 76/16

## TECHNICAL OBJECTIVE

To compare the morbidity and mortality of conservative (non-operative) vs surgical treatment of cortical lacerations analagous to those produced by non-penetrating trauma in man; to compare pre- and post-trauma renal function in these two groups and determine the therapy that provides the maximum preservation of renal function; and to determine the effect of these two therapeutic modalities on the development of hypertension via the renin-angiotensin system.

## METHOD

Ten dogs weighing 25-35 pounds will be used for long term management. These dogs will be divided into two groups (surgical and conservative). Baseline CSC, Na, BUN, creatinines will be drawn. After the induction of anesthesia, pre-trauma urograms will be obtained in addition to urinalysis, urine culture, and blood pressure. Only one renal unit will be studied so that each dog can act as his own control. Trauma will be induced through a flank incision by driving a dull cold chisel one cm into the lower pole cortex to from a cross-shaped laceration. The kidneys will be replaced and a 30 min post-trauma arteriogram will be obtained. The dogs to be treated surgically will undergo heminephrectomy and the remainder will be observed. Three months post-trauma, repeat laboratory studies to include renins, BP, urograms, and arteriograms will be taken. The animals will then be sacrificed and the kidneys examined both grossly and microscopically.

An Investigation to Compare the Effect of Renal Function - Cricco

PROGRESS

(78 10 - 79 09) The initial protocol has been completed. The results look very promising. Consultation with statistician reveals that larger numbers of data must be obtained. Due to the reasignment of all investigators involved in this protocol, no further work is anticipated on this protocol.

STATUS: (C)

TITLE: The Effect of Dimethyl Sulfoxide on the Uptake of Thio-TEPA From the Urinary Bladder of the Dog

PRINCIPAL INVESTIGATOR: CPT Carl F. Cricco, MC

PROFESSIONAL ASSISTANTS: MAJ Eduardo S. Blum, MC
MAJ Willis H. Jacob, MC
MAJ George S. Ward, VC

WORK UNIT NO: 79/57

## TEHCNICAL OBJECTIVE

Thio-TEPA has been used in the management of various types of neoplasias for almost two decades. However, its use in the managment of urinary bladder carcinoma has had mixed results. In addition, the cytotoxic effects of thio-TEPA on the hematopoietic tissues are a severe side effect in its use. The objective of this study is to determine if intravesicular thio-TEPA can be more effectively transported through the urinary bladder wall using DMSO as a carrier.

## METHOD

Ten dogs will be divided into groups I and II (4 dogs each) and Group III (2 dogs). The test solution (50 ml) will be instilled into the urinary baldder of each animal and maintained there for one hour. The test solutions are: Group I - 45 mg thio-TEPA in 50% DMSO; Group II - 45 mg thio-TEPA in an isotonic salt solution; and Group III - 50% DMSO in an isotonic salt solution. The Group III animals are to verify that DMSO does not interfere with thio-TEPA identification.

Blood samples will be obtained from the caudal vena cava and the external jugular vein immediately before instillation of the test solution and at 5, 10, 20, 40, and 60 min after instillation. One blood sample will be taken from a small vein on the bladder surface at 15 min and the test solution will be withdrawn from the bladder at 60 minutes.

Two dogs from Groups I and II will be studied for toxicity following a complete treatment regime, consisting of four weekly treatments as described above. These animals will have bone marrow, liver, kidney, and spleen biopsies before the first treatment. One week following the last treatment, the dogs will be sacrificed and tissue sections of the same

organs plus the urinary bladder and lens will be taken. These tissues will be examined histopathologically for evidence of toxic changes. Complete blood counts will also be performed at weekly intervals.

The remaining two dogs in Groups I and II will have a section of urinary bladder removed following the test solution instillation. This tissue section will be divided and one part homogenized and extracted for thio-TEPA analysis and the other section evaluated histopathologically.

The withdrawn test solution, blood samples, and bladder tissue extracts will be analyzed by spectrophotometry to determine levels of thio-TEPA. The results will be compared to determine effectiveness of DMSO in increasing absorption of thio-TEPA.

## PROGRESS

(79 01 - 79 09) The technical portion of the protocol has been completed and the investigators are awaiting the final analysis of the samples. This analysis has been delayed due to problems with the gas chromatograph.

STATUS: (O)

TITLE: An Evaluation of the Safety and Efficacy of Cyanoacrylate Ester in Ossicular Reconstruction and Nerve Graft Anastomosis in the Guinea Pig Middle Ear

PRINCIPAL INVESTIGATOR: COL William H. Gernon, MC

PROFESSIONAL ASSISTANT: CPT Roy Kim Davis, MC

WORK UNIT NO: 77/88

## TECHNICAL OBJECTIVE

To determine the safety and efficacy of cyanoacrylate ester in the middle ear; specifically, for ossicular reconstruction for histological changes in the oval window area and in the facial nerve. In addition, the use of this compound in tympanoplasty would be a natural extension of this project. The intended purpose of this study is to open the door for the use of cyanoacrylate ester in human surgery, initially on an experimental basis.

## METHOD

The investigators propose to use Histoacryl and Crazy Glue to do interpositions (incus) on a test group of guinea pigs as well as place glue on the facial nerve, perhaps to do facial nerve anastomoses, and to place the glue in the oval window area. Approximately 39 animals would be utilized. At 3, 6, and 12 months, 12 experimental animals and one control animal would be sacrificed. Histological temporal bone studies would then be conducted at AFIP.

## PROGRESS

(78 10 - 79 09) The technique for the surgery has been perfected and six animals have been treated. Of these, two survived and temporal bone pathology is being done at AFIP. Fifteen more animals will be treated in the near future.

STATUS: (O)

TITLE: Medical Treatment of the Frey Syndrome

PRINCIPAL INVESTIGATOR: COL Leonard L. Hays, MC

PROFESSIONAL ASSISTANT: Alvin J. Novack, M.D.
University of Washington

WORK UNIT NO: 76/06

## TECHNICAL OBJECTIVE

1. To study objectively the true incidence of the Frey Syndrome in post-parotidectomy patients by means of the Minor Starch Iodine Test.

2. To determine the effect of, and patient satisfaction with, medical management comparing on a double blind basis topical use of a placebo, varying concentrations of scopolamine hydrobromide, and the newer anticholinergic agent, glycopyrrolate.

3. To investigate the value and practicality of iontophoresis of the above agents to increase the duration of satisfactory control of sweating.

4. To compare the topical use of a patient's most effective antiperspirant on the involved facial skin with the result from the topical use of the most effective agent in the double blind series for that patient.

## METHOD

Phase I - Double-blind treatment with ¼%, 1%, and 3% scopolamine hydrobromide cream, 0.1% glycopyrrolate, and a placebo; comparison by the patient as to effectiveness; and retreatment after drug dosage adjustment if the patient fails to respond.

Phase II - Utilize iontophoretic introduction of the best anticholinergic agent to a group of volunteers with significant sweating symptoms and to a group who are medical failures and compare action and duration of action with iontophoretic introduction using tap water, Ringer's lactate, or saline.

Medical Treatment of the Frey Syndrome - Hays

Phase III - Patients who failed medical treatment or have become dissatisfied with the medical treatment and have significant symptoms confirmed on minor starch-iodine testing will be offered surgery such as flap elevation or tympanic neurectomy.

## PROGRESS

(78 10 - 79 09) Nine patients are continuing intermittant use of glycopyrrolate topically to compare the efficacy of a topical cream to the preparation in roll-on form, plus one new subject has been enrolled in the project. These preparations give excellent control, usually complete, for 2-4 days, but work poorly if the gustatory sweating is heavy in the hairline. There have been no adverse reactions to the use of these agents.

PUBLICATION: Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. The Laryngoscope 88:1796-1824, 1978.

STATUS: (O)

TITLE: Teaching Program for Practical Microsurgery

PRINCIPAL INVESTIGATOR: MAJ Robert Kenevan, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC
LTC David Ekland, MC
MAJ Stanley Jackson, MC
MAJ George Ward, VC

WORK UNIT NO: 77/92

## TECHNICAL OBJECTIVE

To establish a formal training program at Madigan Army Medical Center in clinical microsurgery.

## METHOD

The teaching program will be established at Clinical Investigation Service, and a room will be set aside for the project where equipment for the microsurgery can be housed. A schedule of two afternoons per week will be set aside for teaching sessions. Animal model preparations (cadaver and live) will be developed by the veterinary surgical consultant with the support of the clinical teaching staff. Sessions will begin with lectures, followed by practical exercises in anatomy and step-by-step instruction in the surgical techniques.

## PROGRESS

(78 10 - 79 09) Microvascular anastomoses were practiced until a high patency rate was achieved and the tissue reimplant procedures were begun. During FY 79, 29 guinea pig vascular anastomosis procedures were completed. Four rats and three rabbits were used in six vascular anastomoses and one tissue reimplant.

STATUS: (O)

TITLE: Jejuno-ileal Bypass Surgery for Morbid Obesity

PRINCIPAL INVESTIGATOR: COL Joseph C. McDonald, MC

PROFESSIONAL ASSISTANTS: COL Robert B. Gibbons, MC
LTC Reynaldo G. Geerken, MC
LTC K. David McCowen, MC
MAJ John E. Shoberg, MSC

WORK UNIT NO: 77/81

## TECHNICAL OBJECTIVE

To reduce the morbidity and mortality of morbidly obese patients by achieving weight reduction through partial defunctionalizing of the small bowel. This protocol was activated per a message from HQDA, DASG-HCP, 180800Z, Mar 77.

## METHOD

Subjects must demonstrate a minimum of 100% above ideal body weight; a weight problem for five years; evidence of failure of dietary and/or group therapy measures for weight reduction; age under 50 years; absence of causative endocrine or metabolic dysfunction or unrelated medical disease which would contraindicate operation; presence of complications of obesity; no history of ethanol abuse and a commitment to avoid ETOH for three years postoperatively; mental and emotional stability to tolerate the operation and its postoperative sequelae; and assurance of cooperation in the conduct of necessary pre- and post-operative studies. Once selected for jejuno-ileal bypass, the patient will undergo extensive pre-operative evaluation by the Gastroenterology Service, followed by jejuno-ileal bypass and ileo-cecostomy. Immediate post-operative care will be carried out by the surgeons with appropriate consultation. Long term follow-up will be conducted by each involved service.

## PROGRESS

(78 10 - 79 09) During FY 79 no operations for morbid obesity were performed. It appears that jejuno-ileal bypass has been replaced by gastric plication or bypass as the operation of choice for morbid obesity. At the present time, no further surgery for morbid obesity is planned; therefore, the protocol is terminated.

STATUS: (T)

TITLE: Evaluation of One Stage Longitudinally Reduced Ileal Ureters with the Use of the Auto Suture in Dogs

PRINCIPAL INVESTIGATOR: LTC Robert Modarelli, MC

PROFESSIONAL ASSISTANTS: COL John N. Wettlaufer, MC
LTC Dietrich W. Geschke, MC
LTC Paul B. Jennings, VC

WORK UNIT NO: 77/69

## TECHNICAL OBJECTIVE

To determine the chemical aberrations that occur in the urine and serum between an ileal ureter and its contralateral in situ ureter; to compare quantitatively the changes that occur in the urine of longitudinally reduced ileal ureters and their contralateral in situ ureter; to observe radiographically the function of ileal ureters and longitudinally reduced ileal ureters; to evaluate the applicability of the Auto Suture, Models TA-55 and GIA, in intestinal urinary conduit and urinary bladder surgery; and to study the long-term effects of variably longitudinally reduced ileal ureters on renal function and on qualitative and quantitative changes in urine and serum.

## METHOD

Phase I - divide the urinary bladder in a female dog with the GIS Auto Suture; obtain baseline split renal collections for volume, electrolytes, BUN, creatinine, Ca, phosphorus, protein, glucose, oxalate, pH, and osmolality determinations; obtain simultaneous serum samples for electrolyte, BUN, creatinine, Ca, phosphorus, glucose, and protein determinations; and determine the renal function by excretory urogram.

Phase II - Group I - one ureter will be replaced with a pedicled vascularized distal ileal segment according to techniques used by Goldstein and others. Group II - will have an appropriate segment of ileum isolated on a vascular pedicle. An ileo-ileostomy is carried out to reestablish bowel continuity. The pedicled ileal segment is sutured longitudinally parallel to the mesenteric border of the ileum by applying the TA-55 or GIA Auto Suture, longitudinally bisecting the ileum between its mesenteric and antimesenteric

borders. The sequence is repeated until the ileal segment is longitudinally bisected and a 50% reduction in surface is noted. A proximal ileo-pyelo and a distal ileo-vesicle anastomosis is carried out. Group III - will undergo the same procedure as Group II dogs except that the ileal segment will be reduced to an even smaller lumen, i.e., a 24 French caliber ileal tubular segment.

Qualitative and quantitative split urine collections and serum determinations are repeated as in Phase I in the post-operative period. Radiologic contrast studies, consisting of intravenous pyelograms, retrograde cystograms and fluoroscopic evaluation of the upper and lower urinary tracts, will be done. Urine collections, serum determinations, and radiologic contrast studies will be repeated at 6 weeks, 3, 6, and 12 months post-ureteral replacement surgery. Following initial evaluation of what appears to be the more ideal ileal segment for ureteral replacement, a contralateral nephrectomy will be considered in order to simulate more effectively the patient who has only one functioning kidney remaining. At completion of the investigation, unilateral nephrectomies with hemicystectomies will be performed or the dogs will be sacrificed for gross and microscopic evaluation of kidneys, ileal ureters, and bladder.

## PROGRESS

(78 10 - 79 09) This protocol has been terminated due to the departure of the principal investigator and due to the fact that a prosthesis has been developed to fulfill this function.

STATUS: (T)

TITLE: Lid Magnets for Correction of Orbicularis Palsy

PRINCIPAL INVESTIGATOR: COL Stanley C. Sollie, MC

PROFESSIONAL ASSISTANTS: MAJ Kurt Guelzow, MC
MAJ Frederick A. Mausolf, MC

WORK UNIT NO: 75/27

## TECHNICAL OBJECTIVE

To study the effects of the insertion of lid magnets on the tarsal plates of the lids involved in seventh nerve palsy.

## METHOD

Patients with seventh nerve palsy will be evaluated, and, if the palsy persists longer than six months without showing improvement and if the eye is affected by the lack of lid closures, these patients will be considered for the srugery. The surgery consists of implanting lid magnets, supplied through Wolfgang D. Muhlbauer, Department of Plastic and Reconstructive Surgery, Klinikum rechts der Isar of the Technical University, Munich, Germany. A skin incision is made in the upper and lower lid and the magnets are sutured to the tarsus. The skin incision is then closed.

## PROGRESS

(78 10 - 79 09) No new cases were operated during FY 79. Of the original 7 cases, 3 are doing well, 2 are considered fair, and 2 have been lost to follow-up. The investigators will continue this protocol as new subjects become available.

STATUS: (O)

TITLE: Polymethylmethacrylate, Self Curing Acrylic Cement as a Stimulator of Cellular Immunity

PRINCIPAL INVESTIGATOR: COL Stephen R. Thomas, MC

PROFESSIONAL ASSISTANTS: John P. Heggers, PhD, LTC (Ret)
CPT William A. Bulley, MC
LTC Sam T. Barnes, MC
CPT James B. Talmage, MC

WORK UNIT NO: 75/26

## TECHNICAL OBJECTIVE

To determine if component loosening after total hip replacement where bacterial involvement is not indicated is, in fact, a cellular immune response (tissue rejection phenomenon).

## METHOD

Phase I - Guinea pig stimulation phase in an attempt to promote an immune reaction. Procedure as outlined in protocol.

Phase II - Peripheral blood from two groups of humans will be collected. Group I will be those individuals who have never experienced any surgical procedure which required the use of methylmethacrylate (control group). Group II will be those individuals who have experienced any surgical procedure which required the installation of methylmethacrylate cement.

Ancillary Investigative Procedures - Sheep RBC properly treated as well as polystyrene latex particles could be employed to demonstrate the probable humoral antibody response. Potential development of a microagglutination procedure is feasible.

## PROGRESS

(78 10 - 79 09) - Phase I has been completed on this protocol and a paper has been published (Heggers, J.P., Talmage, J.B., and Barnes, S.T.: Cellular Immune Response to Methylmethacrylate in Experimentally Sensitized Guinea Pigs. Mil Med 143:192-95, 1978). No further work will be performed on this protocol.

STATUS: (C)

TITLE: Symptom Course of Common Cold Syndromes

PRINCIPAL INVESTIGATOR: CPT John P. Armentrout, MC

PROFESSIONAL ASSISTANTS: CPT Michael Halstead, MC
CPT Jerry Sullivan, MC
CPT Debra Walker, ANC

WORK UNIT NO: 79/20

## TECHNICAL OBJECTIVE

To survey the clinical course of various symptoms present in common cold syndromes, as viewed by a primary care physician without the benefit of sophisticated isolation and serological means.

## METHOD

Data collection: Patients aged 5 and over presenting via clinic visit will be asked the duration of a variety of symptoms. If antibiotics are used to treat, that patient is eliminated. The remaining patients will be diagnosed into a major cold group and treated at the discretion of the physician. Positive throat cultures will be treated and remain in the study. The patients will then be contacted in 5-7 days for followup of their symptoms. Complications will be counted, but upon treatment with antibiotics will be terminated from the study. Prolonged courses will be followed until resolution.

Data analysis: Data will be analyzed by age groups and four major diagnostic categories (nasopharyngitis, pharyngotonsillitis, URI, bronchitis). Duration of each symptom will be defined for each group. Days of disability and degree will be analyzed, as well as how many days the patient used medicine. Types and numbers of complications and protracted courses will also be looked at.

## PROGRESS

(78 11 - 79 09) This project has been terminated due to difficulties in setting standards for history taking and reporting of diagnoses, thereby presenting major obstacles in correlation of data.

STATUS: (T)

TITLE: A Medical Information System for Ambulatory Care, Research, and Curriculum in an Army Family Practice Residency: Over 50,000 Patient Problems

PRINCIPAL INVESTIGATOR: MAJ Robert V. Hollison, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 79/51

## TECHNICAL OBJECTIVE

To analyze the demography of the population, the coding scheme, and the major diagnostic problems of 16 months of ambulatory Family Practice data involving over 51,000 patient problems.

## METHOD

Over a 16-month period, the Family Practice Residency at Madigan Army Medical Center coded 51,113 ambulatory problems using the International Classification of Health Problems in Primary Care (ICHPPC) coding scheme. The demography of this defined active duty, retired, and dependent population will be statistically analyzed as will the rank order of the major diagnostic categories and top 25 individual diagnoses.

## PROGRESS

(78 12 - 79 09) The analysis has been completed. The ICHPPC is a valuable tool in the analysis of patient problems. The medical information system developed from this analysis has served many useful purposes at Madigan's Family Practice Residency, i.e., to measure the quality of patient care, as a guide to curriculum development within the Family Practice Residency, and in the realm of patient education whereby patients with identified disease entities can be contacted by mass mailing for the specific purpose of patient education. A manuscript reporting the results of this study has been accepted by the Journal of Family Practice for publication.

STATUS: (C)

TITLE: An Analysis of the Prevalence, Severity, and Correlates of Drug and Alcohol Abuse at a Large Army Installation

PRINCIPAL INVESTIGATOR: John P. Allen, PhD, DAC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/21

## TECHNICAL OBJECTIVE

To provide answers as to the availability of illicit drugs (both on post and in the civilian community); the incidence and nature of illicit durg and alcohol abuse at Fort Lewis and Madigan Army Medical Center; the relationship of substance abuse to social climate, authority relationships, and military preparedness; the relationship to rank, demographic characteristics, abuse-nonabuse characteristics of individuals, etc.; the relationship of alcohol abuse and drug abuse; what characteristics observable by commanders and supervisors define high risk individuals; the psychological/demographic correlates of alcohol-related offenses; the effectiveness of urinalysis as a deterrent; to what groups the ADAPCP can most effectively address its educational/preventive aspects; and what concrete, feasible and promising suggestions can be made to reduce local and Army-wide problems with drug and alcohol abuse.

## METHOD

Sample population will be randomly selected across military ranks on the basis of SSN's and will consist of approximately 3,000 soldiers. After appropriate training, the survey will be administered by battalion adjutants. Data will be submitted to a broad range of correlational and multivariate analyses and will attempt to provide information as stated in the objective section above. Considerable effort will be expended both in data interpretation and in exploration of the preventive health care implications of these statistical analyses. After interpretation of statistical analyses and formulation of action suggestions, the results and proposed course of action will be submitted to Headquarters, 9th Infantry Division and Madigan Army Medical Center (and, if appropriate, to OTSG, HSC, and other higher headquarters). Appropriate information will be disseminated to major subordinate commanders and Alcohol and Drug Dependency Intervention Council.

An Analysis of the Prevalence, Severity, and Correlates of Drug and Alcohol Abuse at a Large Army Installation - Allen

PROGRESS

(78 10 - 79 09) The survey has been completed and analysis of the data is still in progress. Three papers are in preparation for submission for publication.

The survey demonstrated that while no relationship between substance abuse and demographic correlates could be found for officers, age, sex, education, rank, years in service, and occupation were significantly associated with both drug and alcohol abuse among enlisted personnel.

The study measured the relationships between drug abuse, alcohol abuse and concurrent drug and alcohol abuse with three dimensions of military morale; task satisfaction; perceived combat readiness; and interpersonal relationships. Among Army officer personnel and among enlisted personnel who engage only in drug abuse, no relationship was found. Alcohol abuse alone and concomitant drug and alcohol abuse among enlisted are associated with a lower sense of task satisfaction and perceived combat readiness even when the effects of sex, age, rank, education, and years in service on substance abuse are eliminated. The study suggests that those enlisted who engage in both drug and alcohol abuse are higher in interpersonal relationships or camaraderie than those who do not.

STATUS: (O)

TITLE: The Effects of Low Exposure Levels to Anesthetic Gases in Operating Rooms at MAMC

PRINCIPAL INVESTIGATOR: CPT Robert R. Byland, MSC

PROFESSIONAL ASSISTANTS: LTC John Heggers, MSC
MAJ George Ward, VC
CPT Michael Smith, MSC

WORK UNIT NO: 77/72

## TECHNICAL OBJECTIVE

To evaluate the levels of anesthetic gas the anesthesiologist and operating room personnel receive with the present type of gas delivery, recovery, and disposal systems used at this center.

## METHOD

1. Coordinate with OR supervisor and anesthetist as to the length of time various operations take and the gases used.
2. Schedule twelve operations to test for gases.
3. Use previous ventilation survey results for room volume and air turnover rate to predict gas concentrations.
4. Determine prior to any operation the effect of opening and closing of OR doors has on the air flow.
5. Set up the Miran I.R. unit and calibrate.
6. Using the 10-foot sampling hose, collect samples during the operation.
7. Samples will be collected around gas delivery systems, the anesthesiologist, and OR personnel's breathing zones.
8. Samples will be collected every 15 minutes and recorded on a strip chart.
9. Analysis of collected data.

## PROGRESS

(78 10 - 79 09) Coordination with the anesthesiologists has been completed. Monitoring of the operating rooms has been initiated. Rooms will be monitored either with the Miran 1A or with charcoal tubes. All machines will be monitored for leakage with the Miran 1A unit.

STATUS: (O)

TITLE: The Use of Group Process in the Teaching of Family Dynamics to Family Practice Residents

PRINCIPAL INVESTIGATOR: Richard D. Fitzgerald, M.S.W., DAC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 79/52

## TECHNICAL OBJECTIVE

To develop a group process in the teaching of family dynamics to Family Practice Residents that will enhance self-awareness as a physician, personal and professional growth, and understanding of intra and interpersonal dynamics.

## METHOD

An extensive literature search to evaluate the use of group process teaching will be done. Then a program will be planned using the group process method to teach residents the dynamics of family living, and create a better understanding of the Family Practice physician of his patient as he frequently uses himself as the primary therapeutic agent in treating patients. This will be approached by three methods: (1) case consultation, (2) discussion of personal and professional issues and development, and (3) introspection on the group process as it relates to interpersonal and family dynamics. The investigator anticipates a publication on the results of this program and possible implementation of this program at other institutions interested in innovative approaches to medical education.

## PROGRESS

(78 12 - 79 09) This program has been set up at MAMC and has proved to be successful. A manuscript has been submitted for publication.

STATUS: (C)

TITLE: Child Abuse, Job Satisfaction, and Social Isolation Among Military Families

PRINCIPAL INVESTIGATOR: MAJ Larry R. Sanderlin, MSC

PROFESSIONAL ASSISTANTS: LTC Daniel Lanier, MSC, (Ret)
1LT Mario P. Scontrino, MSC, USAR

WORK UNIT NO: 78/06

## TECHNICAL OBJECTIVE

A MAMC sutdy found the child abuse rate to be disproportionately higher among garrison/support troops than among combat infantry soldiers or other soldiers whose jobs require a considerable amount of skill and/or a significant amount of technical training. William Beaumont AMC had similar findings. It is therefore hypothesized that in the military there will be an inverse relationship between child abuse and job satisfaction. It is also hypothesized that there will be a positive correlation between social isolation and child abuse among military families. This study will test these hypotheses.

## METHOD

The study will include three groups with 100 soldiers each.

Group A will come from patients referred to MAMC Social Work Service as the result of child abuse and/or neglect.

Group B will be a matching sample referred for other psychosocial problems, but who are not child abusers.

Group C will be a stratified random sample who have not been identified as having any type of psychosocial problem.

All participants will be asked to complete a Job Description Index and Srole's Anomie Scale to measure social isolation. After the data collection is completed, the results will be analyzed at the University of Washington Academic Computer Center.

## PROGRESS

(78 10 - 79 09) This project has been terminated due to the inability to collect sufficient data.

STATUS: (T)

# SOUTHWEST ONCOLOGY GROUP PROTOCOLS

PRINCIPAL INVESTIGATOR:

LTC FRIEDRICH H. STUTZ, MC

PROFESSIONAL ASSISTANTS:

SURESH KATAKKAR, M.D., DAC

LTC IRWIN DABE, MC

TITLE: M-77-1, Forty-Two Hour Methotrexate Infusions with Citrovorum Rescue - A Clinicopharmacokinetic Analysis (A Phase I-II Study).

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/48

## TECHNICAL OBJECTIVE

To determine the maximal tolerated dose of methotrexate (MTX) which will maintain a constant plasma antifolate concentration for 42 hours.

To identify what clinical factors alter renal clearance of MTX.

To evaluate the antitumor effect of 42-hour MTX infusions with citrovorum.

## METHOD

Patients with any cancer resistant to conventional therapy who meet the other criteria as outlined in the protocol will enter the study in sequence, four patients being treated at each plasma MTX level as outlined in the protocol. A course of treatment will consist of a priming dose of MTX over the first hour, an infusion of MTX over the subsequent 41 hours, and citrovorum factor rescue thereafter, beginning at the time MTX is discontinued. Courses are repeated every two weeks.

At Madigan Army Medical Center this treatment is being used only in patients with tumors that have shown response to it, e.g., sarcoma.

## PROGRESS

(78 10 - 79 09) No patients were entered on this study during FY 79. Three patients were treated in previous years: 1. complete response for 19 months; (2) progressive disease; and (3) lost to follow-up.

STATUS: (O)

TITLE: SWOG 781, Phase III Protocol - Radiotherapy-Chemotherapy (MOPP) for Stages I and II, A and B Hodgkin's

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/55

## TECHNICAL OBJECTIVE

To compare total nodal radiotherapy (TN-XRT) or "mantle" and para-aortic radiotherapy to involved field radiotherapy (IF-XRT) plus MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine) chemotherapy in patients with stages I and II, A and B disease.

## METHOD

Patients with biopsy-proven Hodgkin's disease who have received no prior chemotherapy or radiotherapy and who meet other criteria as outlined in the protocol will be randomized to one of two treatment programs: (1) TN-XRT; (2) IF-XRT followed by MOPP chemotherapy. Following completion of the IF-XRT, a rest period of four weeks will be interposed before chemotherapy is started. Dosages for chemotherapy and radiotherapy and length of courses of treatment as specified in the protocol.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (O)

TITLE: SWOG 7299, Clinical Trial of Radiotherapy and Chemotherapy (Cyclophosphamide, Vincristine, Acto-Dactinomycin, and Adriamycin) in Managing Non-Metastatic Ewing's Sarcoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/89

## TECHNICAL OBJECTIVE

To compare the time interval from clinically localized tumor to appearance of metastases using irradiation of the primary tumor plus systemic chemotherapy or irradiation of the primary tumor plus chemotherapy plus bilateral pulmonary irradiation. To document (a) incidence and time of appearance of local recurrence; (b) the pattern of organ metastases so that future studies will result in programming improved means of therapy; and (c) the total survival time of patients treated by both regimes.

## METHOD

Patient eligibility: all patients with tissue diagnosis of Ewing's sarcoma and no prior therapy and in whom the tumor is localized and the patient is free of demonstrable metastases. Regional involvement, specifically, malignant cells in the spinal fluid, ascitic fluid, and pleural fluid as well as nodal involvement, will be considered metastic.

Treatment: Patients will receive one of two regimens:

Regimen I: Weeks 1-6, irradiation plus vincristine and Cytoxin; Weeks 7-9, rest; Week 10, Dactinomycin; Week 11, rest; Weeks 12-15, vincristine and Cytoxin; Week 16, vincristine and Cytoxin plus adriamycin; Week 17-18, rest.

Regimen II: The same as Regimen I with the addition of bilateral pulmonary irradiation in weeks 4, 5, and 6.

Weeks 10-18 will be repeated eight times to complete the full course of treatment.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (T)

TITLE: SWOG 7410, Chronic Lymphocytic Leukemia Protocol Utilizing Cyclophosphamide, Adriamycin, and Prednisone.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/13

## TECHNICAL OBJECTIVE

1. To determine the response rate, both complete and partial, in chronic lymphocytic leukemia, to combination chemotherapy with:

   A. Cyclophosphamide, adriamycin, and prednisone (CAP) as primary therapy in patients who have had no prior chemotherapy.

   B. CAP as secondary therapy for those patients who have previously received low dose chlorambucil.

2. To assess the effectiveness of intermittent cyclophosphamide and prednisone in maintaining a remission.

## METHOD

After meeting stringent criteria, all untreated patients with CLL or patients previously treated with a low dose of chlorambucil only, at least four weeks prior to start of therapy, will be entered in the study.

Remission Induction: cyclophosphamide - 500 mg/$M^2$, I.V., on day 1
adriamycin - 50 mg/$M^2$, I.V., on day 1
prednisone - 100 mg/day, p.o., for 5 days

After eight courses of induction therapy (or those having attained remission between three & eight courses), those patients who have attained complete or partial remission will receive maintenance therapy consisting of:

cyclophosphamide - 750 mg/$M^2$, I.V., on day 1
prednisone - 100 mg/day, p.o., for 5 days

Course will be repeated every three weeks until relapse in cases in complete remission or increasing disease is evident in cases in partial remission.

## PROGRESS

(78 10 - 79 09) No patients were entered on the study in FY 78.

STATUS: (T)

TITLE: SWOG 7426/27, Chemoimmunotherapy for the Non-Hodgkin's Lymphomas. CHOP-Bleomycin vs CHOP + BCG vs COP + Bleomycin Induction Therapy. No Maintenance vs BCG for Maintenance

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/41

## TECHNICAL OBJECTIVE

1. To compare the effectiveness of two chemotherapy regimens (CHOP + bleomycin) or chemoimmunotherapy (CHOP + BCG) for remission induction in previously untreated patients with non-Hodgkin's lymphomas.
2. To establish baseline and serial data on immunologic status in both chemotherapy and chemoimmunotherapy groups.
3. To evaluate systematic restaging of patients judged to be in complete clinical remission (CR).
4. For patients proven to be in complete remission after induction, to test the value of continued maintenance immunotherapy (BCG) vs no maintenance treatment.
5. For patients who only achieve a partial remission during induction, to test the effectiveness of continued treatment with chemoimmunotherapy.

## METHOD

Patients with any histologic type of stage III or IV non-Hodgkin's lymphoma established by biopsy will be randomized to one of the three induction programs. The schema for the study is given in the protocol. Remission Induction: Eight courses of treatment will constitute remission induction. If induction results in a CR and this is confirmed by restaging, then the patient is eligible for a second randomization into the maintenance phase of this study. If residual lymphoma is detected during restaging, an additional three courses of treatment will be administered, restaging repeated, and patients in CR will be eligible after 11 courses of induction for the maintenance phase. Patients who are only in a partial remission after 11 courses of treatment are eligible for continued treatment with chemoimmunotherapy.

SWOG 7426/27 - Stutz

## PROGRESS

(78 10 - 79 09) No new patients were entered on this study during FY 79. One patient had been treated earlier with partial response.

STATUS: (O)

TITLE: SWOG 7433, Non-Hodgkin's Lymphomas (Stages I, $I_E$, II and $II_E$). A Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/53

## TECHNICAL OBJECTIVE

To compare the remission rate, remission duration, and survival in patients with non-Hodgkin's lymphoma, pathologic stages I, $I_E$, II and $II_E$ treated with extended field radiotherapy (supradiaphragmatic mantle or abdominal field) alone or with extended field radiotherapy plus combination chemotherapy (Cytoxan, Hydroxyl-daunorubicin(adriamycin), Oncovin (vincristine), and prednisone).

## METHOD

Patients newly diagnosed (no type of prior therapy) with non-Hodgkin's lymphoma except mycosis fungoides and diffuse lymphocytic well differentiated lymphoma will be thoroughly evaluated for extent of disease and then randomized to either radiation therapy or radiation therapy plus chemotherapy. If the patient does not achieve a complete remission after completion of his treatment course, he will be removed from the study. Those achieving complete remission will be followed for two years or until relapse.

## PROGRESS

(78 10 - 79 09) No patients were registered on this protocol during FY 79. One patient has been treated in the past with a complete response.

STATUS: (O)

TITLE: SWOG 7436, Combined Modality Therapy of Breast Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/24

## TECHNICAL OBJECTIVE

To compare the effect of two adjuvant chemotherapy programs upon the time to recurrence and upon the percentage of recurrences in post-operative breast carcinoma patients who have a high risk of developing metastases. To compare the effect of these adjuvant chemotherapy programs upon the survival pattern of such patients.

## METHOD

Melphalan and combination (5-Fluorouracil, Methotrexate, Vincristine, Cyclophosphamide, Prednisone) will be used as chemotherapy as outlined in the protocol. The adjuvant chemotherapy will be instituted (regardless of radiation therapy) two weeks after radical mastectomy, unless local or systemic post-operative complications of surgery contraindicate onset of therapy. In such cases, therapy will be instituted when the primary physician involved feels it is not contraindicated by the clinical condition of the patient. The interval between surgery and the institution of adjuvant chemotherapy cannot be greater than six weeks for entry into the study. All therapy will be discontinued after one year.

## PROGRESS

(78 10 - 79 09) Four patients have been treated on this protocol for the one year period and still show complete response. One additional patient was treated and died of CVA before response could be evaluated. This protocol is completed except for continuous follow up of patients. This protocol will be replaced by SWOG protocol 7827.

STATUS: (C)

TITLE: SWOG 7440, Adjuvant Chemotherapy for Osteogenic Sarcoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/17

## TECHNICAL OBJECTIVE

1. To determine the efficacy of combination chemotherapy with CY-VA-DIC (cyclophosphamide, vincristine, adriamycin, and DIC) in preventing the development of metastases in patients with osteogenic sarcoma who have received definitive surgery for their primary lesions and who have no evidence of residual disease.

2. To determine the survival and disease-free interval pattern of patients on this study to be compared to historic controls in the medical literature.

## METHOD

Patients with a confirmed diagnosis of osteogenic sarcoma who have received definitive surgical therapy and have no evidence of metastases following surgery and who have not received any prior therapy (other than surgery) shall be treated with a chemotherapy regimen consisting of vincristine, adriamycin, cyclophosphamide, and DIC as outlined in paragraph 5.0 of the protocol.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this protocol.

STATUS: (O)

TITLE: SWOG 7510, Intensive Adjuvant Chemotherapy with or without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/18

## TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with the highly effective combination of Methyl CCNU (MeCCNU) and 5-Fluorouracil (5-FU) and to determine whether this is added to by immunotherapy with oral Bacillus Calmette-Guerin (BCG) on the disease-free interval and survival of patients with Duke C large bowel adenocarcinoma.

## METHOD

Patients will be randomly assigned to either of the two following regimens:

Chemotherapy alone - Methyl CCNU, given orally on day 1, plus intravenous 5-Fluorouracil, given intravenously weekly for three doses would constitute one course. Courses would begin every eight weeks.

Chemotherapy plus immunotherapy - Chemotherapy as described above plus immunotherapy in the form of oral BCG given every two weeks.

## PROGRESS

(78 10 - 79 09) Nine patients have been treated in previous years on this protocol and are free of evidence of clinical disease. During FY 79, one patient was treated on this protocol with chemotherapy without oral BCG immunotherapy and is in complete remission.

STATUS: (O)

TITLE: SWOG 7517, Therapy of Squamous Cell Carcinoma of the Head and Neck Using Combination Bleomycin, Vincristine, and Methotrexate

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/26

## TECHNICAL OBJECTIVE

To determine the toxicity and effectiveness of various dosage levels of a combination of bleomycin, oncovin, and methotrexate in the treatment of patients with squamous cell carcinoma of the head and neck.

## METHOD

A total of thirty patients with squamous cell carcinoma of the head and neck will be treated with a combination of bleomycin, vincristine, and methotrexate as outlined in the protocol. Patients must receive two complete cycles of therapy to be evaluable for response. The duration of response shall be measured from the time that a partial response is achieved to the time at which progression is apparent.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (O)

TITLE: SWOG 7518, Stage III A and B Hodgkin's Disease Remission Induction by Radiation Therapy Plus Chemotherapy Combination versus Chemotherapy Alone. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/52

## TECHNICAL OBJECTIVE

1. To compare the effectiveness of 10 courses of a five-drug combination chemotherapy (including nitrogen mustard, vincristine, procarbazine, prednisone, and bleomycin) program against the combined three courses of chemotherapy followed by total nodal irradiation therapy program for complete remission induction in patients with Stage III asymptomatic -A or symptomatic -B disease.
2. To evaluate the systematic "restaging" of patients in apparent complete remission.
3. To assess the length of unmaintained remission after intensive induction with ten courses of chemotherapy treatment versus the combination chemoradiation therapy, after documentation of complete remission status by careful "restaging".
4. To assess the toxicity of the chemotherapy alone portion of the study versus the toxicity of the combination of chemotherapy and radiation therapy.
5. To intercompare the results of this program with those to be obtained by SWOG 7406 (ongoing).

## METHOD

Patients with any histopathologic type Stage III Hodgkin's disease and no prior chemotherapy or radiation therapy who meet the other criteria as outlined in the protocol will be randomized to either Treatment 1 or Treatment 2. Treatment 1: chemotherapy alone (nitrogen mustard, vincristine, procarbazine, and prednisone plus bleomycin). Treatment 2: chemotherapy plus radiation therapy (chemotherapy as above followed by total nodal radiotherapy). At the completion of ten courses of chemotherapy or of the total combination chemotherapy, radiation therapy program, a thorough evaluation for evidence of persistent Hodgkin's disease is required. If complete remission is confirmed by this evaluation, no further treatment will be given until relapse occurs. If remission is not confirmed, appropriate treatment will be given on an individual basis.

SWOG 7518 - Stutz

## PROGRESS

(78 10 - 79 09) No patients were treated on this protocol during FY 79. One patient had previously been treated with complete remission.

STATUS: (O)

TITLE: SWOG 7521, Adjuvant Melanoma Protocol

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/38

## TECHNICAL OBJECTIVE

1. To determine the efficacy of BCNU, hydroxyurea, and imidazole carboxamide (BHD) in preventing the recurrence of disease and prolonging the survival of patients with primary malignant melanoma who have received definitive surgical treatment for their primary lesions, have no evidence of residual disease, but in whom by the clinical and pathological characteristics of the primary lesion can be predicted to have a high incidence of recurrence. 2. To determine the efficacy of combination chemotherapy (BHD) with and without BCG in preventing the development of metastases and prolonging the disease-free interval and survival of patients with recurrent malignant melanoma which has been surgically excised ("minimal residual disease"). 3. To determine the immunocompetence of patients with malignant melanoma and any correlation with prognosis. 4. To determine the influence of chemotherapy and chemoimmunotherapy upon the immunocompetence of these patients with malignant melanoma.

## METHOD

Patients who have a histologically confirmed diagnosis of malignant melanoma and have not been previously treated with chemotherapy or radiation therapy and meet the other criteria as outlined in the protocol shall be entered in the study. Patients will be classified as follows for randomization: Class I - localized disease; Class II - regional and solitary distant metastatic disease. Patients with Class I disease will be randomized between BHD and no treatment. Patients with Class II disease will be randomized to either BHD or BHD + BCG. Patients will be treated for one year or until recurrent disease develops. Patients randomized to no treatment will be followed in a similar fashion. After one year of treatment patients are to remain on study and be followed on no treatment.

SWOG 7521 - Stutz

## PROGRESS

(78 10 - 79 09) One patient was randomized to no treatment and failed at 11 months. Another patient is currently under treatment.

STATUS: (O)

TITLE: SWOG 7522, Chemotherapy, Splenectomy With or Without Immunotherapy in the Treatment of Chronic Myelogenous Leukemia. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/78

## TECHNICAL OBJECTIVE

To study the effects of chemotherapy, splenectomy, and/or immunotherapy on leukemic cytogenetics, immune status, appearance of blastic transformation, and any influence in overall survival.

a. To treat and control the early benign phase of chronic myelogenous leukemia with cytoxan, cytosine arabinoside, vincristine and prednisone and to study the influence of chemotherapy on bone marrow morphology, cytogenetics, and leukocyte alkaline phosphatase.

b. To study nonspecific cell mediated immunity prior to and following therapy.

c. To determine if immunotherapy with BCG will augment general immunocompetence of CML patients.

d. To remove extra tumor burden, avoid possible complication of splenic infarction and hypersplenism through surgical splenectomy.

## METHOD

Splenectomy for patients entering this study will be elective. Within each group (splenectomy or no splenectomy) patients will be randomized to receive chemotherapy alone or chemotherapy + BCG immunotherapy. Hence, there will be four groups of patients.

Induction Treatment:

Treatment 1: Cytosar 100 mg/$M^2$ day x 5, subcutaneous
Oncovin 1.0 mg IV day 1
Cytoxan 500 mg/$M^2$ IV day 1
Prednisone 100 mg PO day x 5
Tice BCG scarification on days 8 and 15

Treatment 2: COAP only (same dosages as for Treatment 1)

Following three courses of induction treatment, patients will be evaluated for splenectomy. For patients not undergoing splenectomy, maintenance chemotherapy will be initiated. Splenectomy will be planned during days 21-28 after COAP #3, when the peripheral circulating WBC is between 5 and 20,000/$mm^3$.

SWOG 7522 - Stutz

Maintenance Treatment

Treatment 1: Hydroxyurea PO in 4 divided dosages daily.
Dosage depends upon the WBC.
BCG weekly between hydroxyurea courses.

Treatment 2: Hydroxyurea PO in 4 divided dosages daily.

PROGRESS

(78 10 - 79 09) No patients were treated on this protocol during FY 79. In previous years, one patient expired the day after entry and another patient expired eight days after entry.

STATUS: (O)

TITLE: SWOG 7524, Chemotherapy in Stages III & IV Ovarian and Endometrial Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/28

## TECHNICAL OBJECTIVE

Primary: 1. To compare the effectiveness of chemotherapy alone (adriamycin-cyclophosphamide) vs chemoimmunotherapy (adriamycin-cyclophosphamide plus BCG) for remission induction in patients with Stages III and IV ovarian and endometrial carcinoma who have had no previous cytotoxic chemotherapy.
2. To test the effectiveness of continued chemoimmunotherapy vs chemotherapy in maintaining complete remissions (documented) achieved during the initial 12-month induction therapy.
3. To test the effectiveness of continued chemoimmunotherapy vs chemotherapy in inducing complete remissions or maintaining partial remissions in patients with occult disease at the time of restaging for complete response or in patients achieving only partial clinical remission during the initial 12-month induction therapy.

Secondary: 1. To establish baseline and serial data on immunologic status in both chemotherapy and chemoimmunotherapy groups.
2. To evaluate systematic restaging of patients judged to be in complete clinical remission.

## METHOD

Patients meeting the criteria will be randomized to two treatment plans for both remission induction and maintenance. Treatment 1 will consist of adriamycin and cytoxan; treatment 2 will consist of adriamycin and cytoxan plus BCG. For maintenance, treatment 1 will consist of cytoxan, and treatment 2 will consist of cytoxan plus BCG. Twelve courses of treatment will constitute the remission induction phase of the protocol. If residual tumor is detected following the 12 courses of therapy, BCG plus cyclophosphamide for the chemoimmunotherapy patients or cyclophosphamide alone for the chemotherapy patients may be continued at 4-week intervals until a total of 2 years of therapy has been achieved

or there is documented evidence of recurrence or progression of disease. Those patients who have no detectable post-induction disease or who have occult disease or only clinical partial responses after the initial 12 courses of induction therapy are to be continued on maintenance therapy as outlined in the protocol.

PROGRESS

(78 10 - 79 09) No patients have been entered on this study and it has been terminated.

STATUS: (T)

TITLE: SWOG 7603, Effect of Schedule on Activity of 5-Azacytidine in Acute Leukemia. Phase III Protocol

PRINCIPAL INVESTIGATOR: LTC FRIEDRICH H. STUTZ, MC

WORK UNIT NO: 77/39

## TECHNICAL OBJECTIVE

This study will compare the activity and toxicity of single dose vs continuous 5-day infusions of 5-azacytidine in patients with acute leukemia.

## METHOD

Patients will be randomized to one of the following regimens:

1. Single day infusion of 750 mg/$M^2$. 5-azacytidine will be given in 3 divided doses (250 mg/$M^2$ administered in 200 ml of Ringer's lactate solution over 2 hours) at 4 hour intervals (2 hours on therapy, 2 hours off therapy).

2. Five day infusion of 300 mg/$M^2$/day. 5-azacytidine will be administered in 4 divided doses in 200 ml Ringer's lactate solution as a continuous infusion over each 6 hour period. Each 6 hour dose should be prepared within 2 hours before use, and preferably immediately before administration.

Courses will be repeated at 3 week intervals unless the bone marrow cellularity remains less than 10%. The dosage of subsequent courses of 5-azacytidine will be based upon the patient's response to the previous course.

## PROGRESS

(78 10 - 79 09) No new patients were entered on this protocol during FY 79. One patient had been studied earlier, but expired too early (after three days) for response.

STATUS: (O)

TITLE: SWOG 7610, Chemotherapy of Disseminated Testicular Cancer with Vinblastine, Bleomycin, Cis-Diammine-dichloroplatinum, Chlorambucil, and Actinomycin-D

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/19

## TECHNICAL OBJECTIVE

1. To determine the effectiveness of the drug combination, vinblastine, bleomycin, and Cis-diamminedichloroplatinum (II) (CACP) in the remission induction of disseminated testicular carcinoma.

2. To determine the duration of remission with a maintenance drug combination of chlorambucil and actinomycin-D, alternating with vinblastine.

## METHOD

All patients meeting criteria as outlined in the protocol are to receive vinblastine, bleomycin, and CACP for two months. At that point, patients judged to be in complete remission, partial remission, or stable will receive an additional two months of therapy All partial and complete responders at four months will then enter the remission maintenance program. Patients with increasing disease at two months, or stable or increasing disease at four months are to be taken off study.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study. It has been replaced by SWOG protocol #7817.

STATUS: (T)

TITLE: SWOG 7613, Combination Chemotherapy for Advanced Soft Tissue Sarcomas Utilizing Adriamycin, DIC, Cyclophosphamide and Dactinomycin. Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/34

## TECHNICAL OBJECTIVE

To determine the maximal effective chemotherapy induction regimen for patients with disseminated soft tissue sarcomas who have probability of response $\geq$50%. To determine if cycling the use of adriamycin and maintenance with CY-DIC-DACT increases the duration of CR's treated initially with A-DIC.

## METHOD

Patients with biopsy confirmed diagnosis of soft tissue sarcoma with evidence of metastatic disease, who meet the other criteria as outlined in the protocol, will be stratified according to adequate or inadequate marrow reserve. These groups will then be randomized to receive adriamycin + DIC; adriamycin + DIC + Cytoxan; or adriamycin + DIC + Dactinomycin, in dosages as specified in the protocol. For both adequate and inadequate bone marrow reserve patients, a complete cycle of chemotherapy shall be repeated every 22 days, counting the first day of therapy as day 1. If on day 22 the white blood count is still less than 2,000 and/or platelet count still below 75,000, the start of the next course shall be delayed until these levels have been reached. In addition a new cycle of chemotherapy shall not be initiated unless stomatitis from previous therapy has been resolved. Dose changes and continuation of treatment shall be determined on an individual patient basis.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (T)

TITLE: SWOG 7618, Combined Preoperative Adjuvant Therapy in Rectal Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/58

## TECHNICAL OBJECTIVE

1. To determine if adjuvant preoperative irradiation and combination chemotherapy will yield a higher incidence than expected of Duke A lesions in a high risk group of patients with rectal carcinoma.
2. To determine the survival of patients with rectal carcinoma, both those with and without regional node metastasis, following the combined treatment stated in #1.

## METHOD

Patients with histologically proven carcinoma of the rectum who meet the other criteria as listed in the protocol will be randomized to one of two treatment modalities: (1) radiotherapy followed by surgery; (2) radiotherapy and chemotherapy followed by surgery. For both treatment arms, the preoperative irradiation and surgery will be identical. Radiotherapy: 2000 rads at the rate of 1000 rads per week, five treatments per week. Chemotherapy: mitomycin-C, 10 mg/$M^2$, given once IV through a running IV as a bolus injection, or a 20-30 minute infusion; 5-fluorouracil 1000 mg/$M^2$/day as a continuous 24 hour infusion via a central venous pressure indwelling intracath for 4 days. Both 5-fluorouracil and mitomycin will be started on the first day within eight hours of the completion of the first radiation treatment. The 4-day 5-fluorouracil administration will be repeated starting on day 28. The patient will undergo an abdominoperineal resection 6-8 weeks after completion of the radiotherapy.

## PROGRESS

(78 10 - 79 09) No patients were treated on this protocol during FY 79. Previous to FY 79, one patient had been treated for 18 months with complete remission.

STATUS: (T)

TITLE: SWOG 7620, Treatment of Early Squamous Cell Carcinoma of the Head and Neck with Chemotherapy or Chemoimmunotherapy Following Initial Surgery and/or Radiotherapy

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/35

## TECHNICAL OBJECTIVE

To determine if the disease-free interval and survival of patients in high risk categories of squamous head and neck cancer can be improved by adjuvant chemotherapy or chemoimmunotherapy after initial surgery, radiotherapy, or combination approach have resulted in no clinically evident disease. To accumulate immunologic data in treated and untreated patients with this malignancy.

## METHOD

Patients will be registered and randomized after the reaction from the initial operative or radiotherapeutic intervention has settled and when they have achieved no clinically evident disease. The randomization process must be accomplished no later than three months after the completion of the surgery or irradiation. The tumor will be stratified into one of the four broad anatomic regions: oral cavity, larynx, pharynx, nasal cavity, and paranasal sinuses. The control group will receive no further therapy after initial surgery and/or irradiation. The chemotherapy group will consist of methotrexate 12 mg/$M^2$ IM daily x 3 days every 21 days for one year. The chemotherapy-immunotherapy arm will consist of methotrexate 12 mg/$M^2$ IM daily x 3 days every 21 days for one year with BCG scarifications administered on day 8 and 14 for eight doses of BCG. Following eight doses, the BCG may then be administered on day 14 only and continued for the remainder of the year. BCG will not be applied to the neck.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (O)

TITLE: SWOG 7622, Combined Modality for Mycosis Fungoides -- Stage I (Phase II)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/60

## TECHNICAL OBJECTIVE

1. To compare the effectiveness of combined electron beam therapy and adjuvant chemotherapy vs electron beam therapy alone for patients with Stage I mycosis fungoides to determine the time to recurrence and to determine the percentage of recurrence.
2. To determine the effectiveness of adjuvant chemotherapy and survival patterns of such patients.
3. To determine the value of staging laparotomy in the management of mycosis fungoides.

## METHOD

Patients who have two or more skin biopsies read as mycosis fungoides by a pathology panel and who meet other criteria as listed in the protocol will be randomized to receive electron beam therapy alone or electron beam therapy and adjuvant chemotherapy. Electron beam total body irradiation will be given via the Stanford Technique to a dose of 3000-5000 rads/40-60 days. Following the completion of electron beam therapy a rest period of four weeks is completed before chemotherapy is started. Chemotherapy will consist of: Cytoxan, 450 mg/$M^2$ IV on day 1 only; adriamycin, 30 mg/$M^2$ on day 1 only; vincristine, 1.4 mg/$M^2$ on day 1; prednisone, 100 mg orally for 5 days; and bleomycin, 2 units/$M^2$ IV 30" after vincristine on day 1. A total of 8 cycles at 3-week intervals will be delivered. Patients will be followed indefinitely or to a point of relapse.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (O)

TITLE: SWOG 7624, ADR vs ADR+CACP in Transitional Cell Bladder Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/30

## TECHNICAL OBJECTIVE

To compare the efficacy of adriamycin vs adriamycin plus cis-diamminedichloroplatinum (II) in recurrent or disseminated transitional cell bladder carcinoma.

## METHOD

Patients with histologically proven transitional cell bladder carcinoma, who meet other criteria as outlined in the protocol, will be randomized to receive ADR alone or ADR+CACP. ADR will be given in a dose of 50 mg/$M^2$ IV on day 1 of each course for Treatment Plan I. On Treatment Plan II, adriamycin will be given in a dose of 50 mg/$M^2$ IV on day 1 of each course; CACP will be given in a dose of 50 mg/$M^2$ IV on day 2 of each course; immediately prior to the administration of CACP, the patient is to be given an IV injection of 12.5 grams of Mannitol. An adequate trial will be two courses. All patients must be observed for a minimum of six weeks. Courses will be repeated every three weeks.

## PROGRESS

(78 10 - 79 09) In previous years two patients have been treated on this protocol. One was treated for six months before expiration. One was treated for two courses with good partial response before going off protocol. No patients were treated during FY 79 and the protocol has been terminated.

STATUS: (T)

TITLE: SWOG 7625, Combination Chemotherapy for Advanced Sarcomas of Bone and Mesothelioma Utilizing Rubidazone and DIC (Dimethyl Triazeno Imidazole Carboxamide)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/61

## TECHNICAL OBJECTIVE

1. To determine the efficacy in terms of rate of response of combination chemotherapy with the 2-drug regimen RubiDIC (Rubidazone + DIC) in patients with metastatic sarcomas of bone and mesothelioma.
2. To determine the duration of remission and survival pattern of patients on this study and compare them with that of patients with metastatic bone sarcomas and mesothelioma on previous Southwest Oncology Group or M.D. Anderson Hospital protocols using adriamycin containing regimens.
3. To determine the toxicity of the regimen especially with regard to cardiac toxicity.

## METHOD

Patients with a biopsy-confirmed diagnosis of bony sarcoma or mesothelioma with measurable metastases who have already received appropriate surgical therapy, who have not received prior adriamycin, daunorubicin, rubidazone, DIC, or BIC, and who meet other criteria as outlined in the protocol will be entered in the protocol on two treatments. Treatment I (adequate marrow reserve) will consist of rubidazone, 150 mg/$M^2$ IV on day 1 and DIC, 250 mg/$M^2$/day IV on days 1-5 inclusive. Treatment II (inadequate marrow reserve) will consist of rubidazone, 120 mg/$M^2$ IV on day 1 and DIC, 200 mg/$M^2$/day IV on days 1-5 inclusive. For both treatments, a complete cycle of chemotherapy shall be repeated every 22 days. Patients who remain in complete remission having received a total of two years of chemotherapy will have the chemotherapy discontinued, but will continue to be followed.

## PROGRESS

(78 10 - 79 09) No patients have been registered on this protocol.

STATUS: (O)

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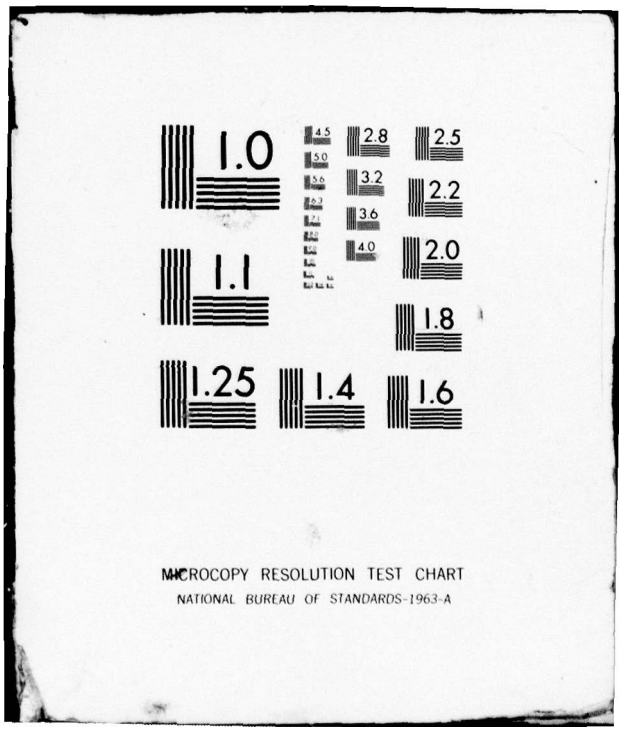
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TITLE: SWOG 7628, Combined CT/RT/IT for Oat Cell Cancer of the Lung (Chemotherapy, Radiation Therapy, Immunotherapy).

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/46

## TECHNICAL OBJECTIVE

1. To use combination chemotherapy, local radiotherapy, and maintenance chemotherapy or chemoimmunotherapy in the treatment of oat cell carcinoma of the lung in order to improve the quality of survival and the duration of survival.
2. To compare the effectiveness of two combination chemotherapy induction regimens in a randomized fashion prior to radiotherapy of the primary.
3. To test the effectiveness of continued chemoimmunotherapy vs chemotherapy in maintaining complete or partial remissions.
4. To test the effectiveness of continued immunotherapy vs no maintenance treatment in patients achieving long-term complete remissions.
5. To establish baseline and serial data on immunologic status in both chemotherapy and chemoimmunotherapy groups.

## METHOD

Patients with histologically proven diagnosis of oat cell carcinoma or small cell undifferentiated carcinoma of the lung with no prior chemotherapy or radiotherapy, who meet the other criteria as outlined in the protocol, will be entered on this study. Patients will be randomized into four treatment arms with different combinations of CT, RT, and IT as specified in the treatment plan of the protocol. Cyclophosphamide, vincristine, methotrexate, 5-fluorouracil, and adriamycin are the drugs to be used. BCG vaccine will be used for immunotherapy.

## PROGRESS

(78 10 - 79 09) On patient was treated for six months with complete response when she developed a new primary (breast) carcinoma. In previous years, two patiets were treated for less than one month each. Both had significant progression while on treatment.

STATUS: (C)

TITLE: SWOG 7632, Combined Modality Protocol for Recurrent Breast Cancer, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/63

## TECHNICAL OBJECTIVE

1. To establish the survival of breast cancer patients when treating the first recurrence with a coordinated hormonal chemotherapeutic approach.

2. To determine the efficacy of a response to the antiestrogen Tamoxifen in predicting response to ablative surgery.

3. To correlate hormonal manipulations with estrogen and progesterone receptors where possible.

## METHOD

First recurrence patients who have been surgically and/or radiotherapeutically treated with the intent of cure of their primary disease and who meet other criteria as outlined in the protocol will be divided into two groups. Group I (no prior castration) will receive Tamoxifen, 10 mg BID, followed by castration plus Tamoxifen. Responding patients will subsequently undergo adrenalectomy or hypophysectomy; nonresponding patients will receive chemotherapy. Group II (prior castration) will start on Tamoxifen. Responding patients will after relapse go directly to adrenalectomy or hypophysectomy; nonresponding patients will go directly to chemotherapy. Surgical guidelines and chemotherapy as outlined in protocol.

## PROGRESS

(78 10 - 79 09) Two patients have been treated on this protocol.

Patient I: on treatment 8+ months - stable disease.

Patient II: On treatment 4 months. Mixed response - decrease of chest wall nodules; development of pericardial metastasis. Patient died five months after she was taken off the protocol with progressive disease.

During FY 79, no new patients were registered on this study.

STATUS: (O)

TITLE: SWOG 7634, Evaluation of MeCCNU Plus B-2'-Deoxythioguanosine and Mitomycin-C Plus B-2'-Deoxythioguanosine in the Treatment of Refractory Disseminated Colorectal Carcinoma. Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/65

## TECHNICAL OBJECTIVE

1. To evaluate the effectiveness of MeCCNU plus B-2'-deoxythioguanosine (BTGdR) for remission induction in disseminated colorectal carcinoma for patients failing to respond or relapsing from chemotherapy with Mitomycin-C plus 5-FU or Mitomycin-C plus Ftorafur, 5-FU alone, or Ftorafur alone.
2. To evaluate the effectiveness of MITO-C plus BTDdR for remission induction for patients failing to respond or relapsing from chemotherapy with MeCCNU plus 5-FU of MeCCNU plus Ftorafur, 5-FU alone, or Ftorafur alone.

## METHOD

Patients with histologically proven disseminated colorectal carcinomas who meet the other criteria as outlined in the protocol will be treated as follows:

Treatment 1: Patients with prior exposure to MeCCNU + 5 FU or MeCCNU + Ftorafur, 5-FU alone or Ftorafur alone.

Good risk: MITO-C, 15 mg/$M^2$ IV days 1 and 56
BTGdR, 60 mg/$M^2$ days 1-5, 28-32, 56-60

Poor risk: MITO-C, 10 mg/$M^2$ IV on days 1 and 56
BTGdR, 50 mg/$M^2$ on days 1-5, 28-32, 56-60

Treatment 2: Patients with prior exposure to Mitomycin-C + 5-FU or Mitomycin + Ftorafur, 5-FU alone or Ftorafur alone.

Good risk: MeCCNU, 130 mg/$M^2$ PO on days 1 and 56
BTGdR, 60 mg/$M^2$ on days 1-5, 28-32, 56-60

Poor risk: MeCCNU, 100 mg/$M^2$ PO on days 1 and 56
BTGdR, 50 mg/$M^2$ on days 1-5, 28-32, and 56-60

Patients without prior exposure to MeCCNU or Mitomycin-C will be randomized to receive Treatment I or Treatment II.

SWOG 7634 - Stutz

## PROGRESS

(77 10 - 78 09) Four patients were treated for 2, 3, 5, and 6 months respectively. All patients had progressive disease while on treatment. The first patient expired.

(78 10 - 79 09) No new patients were registered on this protocol.

STATUS: (O)

TITLE: SWOG 7635, Combined Modality Treatment of Limited Squamous Carcinoma of the Lung. Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/82

## TECHNICAL OBJECTIVE

1. To determine whether chemotherapy with adriamycin and/or immunotherapy with levamisole improve median survival of split-course radiotherapy used alone in the treatment of patients with limited extent squamous bronchogenic carcinoma.

2. To determine the qualitative and quantitative toxicity of each treatment regimen.

## METHOD

Patients with a histologically confirmed diagnosis of limited squamous carcinoma of the lung with no previous chemotherapy or radiation therapy will be randomized to one of the following regimens:

Regimen A: Radiation therapy plus levamisole.
Regimen B: Radiation therapy plus adriamycin.
Regimen C: Radiation therapy plus adriamycin and levamisole.
Regimen D: Radiation therapy alone.

## PROGRESS

(78 10 - 79 09) No patients entered on this protocol during FY 79. In the previous year, one patient was registered, but was never treated because he was found, on tomograms, to have metastatic disease after registration, but before the start of treatment.

STATUS: (O)

TITLE: SWOG 7639, Two Adriamycin, Mitomycin C and 5-Fluorouracil Combinations in the Management of Gastric Adenocarcinoma. A Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/66

## TECHNICAL OBJECTIVE

1. To determine and to document both the response rates and the toxicities of two different combinations of adriamycin, mitomycin C and 5-fluorouracil in the management of surgically incurable adenocarcinoma of the stomach.
2. To compare the effectiveness of these two regimens.

## METHOD

Patients who have unresectable gastric adenocarcinoma and an objectively measurable lesion with no prior exposure to adriamycin, daunomycin, mitomycin C, or porfiromycin, and who meet other criteria as outlined in the protocol will be randomized to one of the two treatments.

Treatment 1: sequential regimen
adriamycin, 50 mg/$M^2$ day 1
mitomycin C, 10 mg/$M^2$ day 3
5-fluorouracil, 600 mg/$M^2$ day 29

Treatment 2: simultaneous regimen
adriamycin, 30 mg/$M^2$ per dose, day 1 and 19
mitomycin, 10 mg/$M^2$ day 1
5-fluorouracil, 600 mg/$M^2$ per dose, day 1,8,29, 36

Although one single course of therapy (8 weeks on study) would be considered as an adequate trial, an attempt should be made to administer at least two courses of therapy where possible. Patients whose disease has remained stable or has regressed on therapy will be continued on this combination for a total of two years unless the adriamycin dose limitation or drug toxicity precludes such continuation of therapy.

SWOG 7639 - Stutz

## PROGRESS

(77 10 - 78 09) One patient was entered on the protocol for four months with progressive disease while on treatment.

(78 10 - 79 09) No new patients were registered on this protocol.

STATUS: (O)

TITLE: SWOG 7701, CCNU, Ifosfamide, Adriamycin (CIA) vs. Ifosfamide - Adriamycin vs. Ifosfamide in Extensive Non-Oat Cell Lung Cancer with Methotrexate Added to Maintenance. Phase III Study.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/83

## TECHNICAL OBJECTIVE

1. To determine if ifosfamide, adriamycin, and CCNU is a more effective combination than ifosfamide alone or in combination with adriamycin in the treatment of patients with extensive non-oat cell carcinoma of the lung who are not eligible for curative radiotherapy.

2. To measure the relative efficacy of this regimen on survival.

3. To determine the qualitative and quantitative toxicity of the regimen.

4. To compare response induction.

## METHOD

Eligibility criteria: All patients with a histologically confirmed diagnosis of extensive non-oat cell carcinoma of the lung, provided they have received no previous chemotherapy.

Stratification by - prior x-ray therapy; then by Karnofsky Performance Status. The patients will be randomized within each of the six stratification groups to receive on of the three treatments:

Treatment 1 - Ifosfamide 1 gm/$M^2$ days 1-5, then once weekly
Adriamycin 40 mg/$M^2$ day 2, then once q 3 weeks
CCNU 65 mg/$M^2$ PO day 3, then once q 8 weeks

Treatment 2 - Ifosfamide 1 gm/$M^2$ days 1-5, then once weekly
Adriamycin 40 mg/$M^2$ day 2, then once q 3 weeks

Treatment 3 - Ifosfamide 1 gm/$M^2$ days 1-5, then once weekly

Ascorbic acid is given 250 mg PO tid and 500 mg hs during the loading course and 250 mg tid on the days of ifosfamide therapy during maintenance.

SWOG 7701 - Stutz

Maintenance Therapy: Maintenance therapy begins 3 weeks after the last dose of adriamycin (cummulative dose of 450 mg/$M^2$). Ifosfamide continues to be given weekly. CCNU continues to be given every 8 weeks. Methotrexate is given in a dose of 30 mg/$M^2$ i.m. and repeated every 4 weeks.

## PROGRESS

(77 10 - 78 09) One patient was treated with ifosfamide for one month and had pregressive disease while on treatment.

(78 10 - 79 09) No new patients were registered on this protocol during FY 79. It has been replaced by SWOG protocols 78/07 and 78/32.

STATUS: (T)

TITLE: SWOG 7703, Radiation Therapy in Combination with BCNU, Dimethyl Triazeno Imidazole Carboxamide (DTIC) or Procarbazine in Patients with Malignant Gliomas of the Brain. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/74

## TECHNICAL OBJECTIVE

To compare the effectiveness of radiation therapy plus BCNU, radiation therapy plus DTIC, and radiation therapy plus procarbazine for remission induction, duration of remission, and survival in patients with malignant gliomas of the brain.

## METHOD

Patients with histologically confirmed primary central nervous tumors of the following histologic types will be entered on the study: astrocytoma, grades 3 and 4 (glioblastoma multiforme). Other criteria: surgery with histologic diagnosis within the prior four weeks and no prior chemotherapy of any type with the exception of corticosteroids. Patients will be randomly allocated to one of the three programs: (1) radiation therapy plus BCNU; (2) radiation therapy plus procarbazine; (3) radiation therapy plus DTIC (dosage as outlined in the protocol). Since survival time is an important end point of this study, each investigator will be required to follow each patient until death and to report the death.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this protocol.

STATUS: (O)

TITLE: SWOG 7704, Chemoimmunotherapy for Multiple Myeloma - VMCP + VCAP vs VMCP-VBAP vs MP for Remission Induction Therapy: VMCP vs VMCP + Levamisole for Maintenance After Remission Induction. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/75

## TECHNICAL OBJECTIVE

1. To compare the effectiveness of three intermittent pulse chemotherapy combinations, VMCP + VCAP vs VMCP + VBAP vs MP for induction of remissions in previously untreated patients with multiple myeloma. (V = vincristine, M = melphalan, C = cyclophosphamide, P = prednisone, A = adriamycin, B = BCNU, L = levamisole) Results will also be compared with other combination chemotherapy treatments in previous SWOG studies, especially VMCP treatment in SWOG 7418 and previous studies of MP combinations.
2. For patients proven to have at least a 75% tumor regression after induction, to compare the value of 12 months of chemoimmunotherapy maintenance VMCP + Levamisole in comparison to VMCP alone.
3. To establish baseline and serial data on immunologic status in these patient groups.

## METHOD

Patients with previously untreated multiple myeloma who meet other criteria as outlined in the protocol will be randomized to one of the following treatments. For induction:

Treatment 1: regular alternating combinations VMCP (1 cycle) then VCAP (1 cycle) alternating q 3 weeks
Treatment 2: sequential alternating combinations VMCP (3 cycles) then VBAP (3 cycles)
Treatment 3 single combination - MP 3 week cycles

For maintenance:
Treatment 1: VMCP
Treatment 2: VMCP + Levamisole

Patients still in remission at the end of 12 months of maintenance with either VMCP or VMCP plus levamisole will be followed in an unmaintained remission state. Upon relapse from unmaintained

remission, patients should be reinduced with the previously used maintenance treatment and this program should be continued until relapse.

## PROGRESS

(77 10 - 78 09) Two patients have been entered on this protocol.

Patient I: On treatment 13+ months - in complete remission.

Patient II: On treatment 6 months - partial remission.

(78 10 - 79 09) One new patient was entered during FY 79 and is presently in clinical remission.

This protocol has been terminated.

STATUS: (T)

TITLE: SWOG 7706, Combination Chemotherapy for Stages III and IV Ovarian Carcinoma Resistant to Adriamycin-Cyclophosphamide Treatment of Single Alkylating Agent Treatment

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/08

## TECHNICAL OBJECTIVE

1. To use a combination of 5-FU, hexamethylmelamine, and platinum in an attempt to induce complete and partial clinical remissions in patients with stages III and IV ovarian carcinoma which have failed to respond to or have relapsed following remission from adriamycin-cyclophosphamide therapy.

2. To use a combination of 5-FU, hexamethylmelamine, platinum, and adriamycin to induce complete and/or partial remissions in patients with stages III and IV ovarian carcinoma who have failed on or relapsed from previous alkylating agent therapy.

## METHOD

Patient Eligibility: (1) diagnosis of ovarian carcinoma established by biopsy; epithelian type neoplasms to be included; (2) only patients with pathologic stages III or IV ovarian carcinoma are eligible; patients who have relapsed after initial radiation therapy will not be eligible; (3) only patients who had previously received and had failed or relapsed following adria-CTX therapy or those having previous single alkylating agent chemotherapy will be eligible; (4) patients with a history of serious cardiac arrhythmias, myocardial infarction, or congestive heart failure will be ineligible to receive adriamycin and should be placed on the three drug regimen (cis-platinum, hexamethylmelamine, 5-FU); (5) patients with serum creatinines >1.5 mg%, BUN's >25 mg%, and creatinine clearances of <60 mg/min or obstruction to the ureters seen on IVP are ineligible for cis-platinum and should be placed on adriamycin, 5-FU, and hexamethylmelamine where appropriate; (6) measurable residual tumor is required for entry; (7) WBC must be >2,500 and platelets >100,000/mm. BUN should be 25 mg%, and serum creatinine <1.5mg%. Creatinine clearance of $\geq$60 and no obstruction to the ureters by IVP.

SWOG 7706 - Stutz

Initial drug doses will be based on bone marrow reserve.

Treatment 1: Patients who have failed to respond to or relapsed from prior adriamycin-CTX.

| | |
|---|---|
| 5-fluorouracil | 400 mg/$M^2$ IV on days 1 & 8 |
| hexamethylmelamine | 150 mg/$M^2$ PO daily days 1-14 |
| plus pyridoxine | 50 mg qd days 1-14 |
| cis-platinum | 50 mg/$M^2$ IV infusion (1 mg/min) day 1 |

Treatment 2: Patients who have previously failed on or have relapsed following therapy with single alkylating agent therapy.

| | |
|---|---|
| adriamycin | 25 mg/$M^2$ IV on day 1 |
| 5-fluorouracil | 300 mg/$M^2$ IV days 1 & 8 |
| hexamethylmelamine | 150 mg/$M^2$ PO days 1-14 |
| plus pyridoxine | 50 mg qd, days 1-14 |
| cis-platinum | 50 mg/$M^2$ (1 mg/min) day 1 |

PROGRESS

(78 02 - 78 09) One patient was on treatment for eight months with good partial remission.

(78 10 - 79 09) No new patients were registered on this protocol during FY 79.

STATUS: (O)

TITLE: SWOG 7707, Chemotherapy of Previously Treated Lymphoma Patients Using VBAP

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/15

## TECHNICAL OBJECTIVE

To evaluate the frequency and completeness of response to VBAP chemotherapy (vincristine, BCNU, adriamycin, prednisone) in patients with malignant lymphoma (non-Hodgkin's disease and Hodgkin's disease) who have received prior therapy and are not eligible for higher priority studies.

## METHOD

Patient Eligibility: Patients who have Hodgkin's disease or non-Hodgkin's lymphoma with measurable tumor and who have become refractory to prior treatment and are ineligible for higher priority. Patients should not have received prior myelosuppressive therapy for at least three weeks prior to this study. Prior nitrosourea or adriamycin therapy does not exclude patients so long as the cumulative dose of adriamycin does not exceed 390 mg/$M^2$. If prior therapy with vincristine resulted in permanent neurotoxicity, this agent will be deleted. Patients with history of myocardial disease are ineligible.

Treatment: These courses will be given in 21-day intervals if the blood counts are no lower than at onset of treatment:

| VBAP | DAY: 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Vincristine (total dose) IV | 1 mg | | | |
| BCNU mg/$M^2$ IV | 30 | | | |
| Adriamycin mg/$M^2$ | 30 | | | |
| Prednisone mg/$M^2$, PO | 60 | 60 | 60 | 60 |

The program will be continued so long as there is stable or improving disease. Adequate trial is two courses. Should remission be achieved then the medications wil continue to maximum adriamycin tolerance (450 mg/$M^2$).

SWOG 7707 - Stutz

PROGRESS

(78 05 - 78 09) One patient on protocol for 5 months with partial response.

(78 10 - 79 09) No patients were treated on this protocol.

STATUS: (O)

TITLE: SWOG 7713/14, Chemoimmunotherapy in Non-Hodgkin's Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy: Levamisole vs No Maintenance after Remission Induction

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/02

## TECHNICAL OBJECTIVE

1. To compare the effectiveness, in terms of rate of response of two chemoimmunotherapy regimens (CHOP + levamisole vs CHOP + levamisole + BCG) against CHOP for remission induction in previously untreated patients with non-Hodgkin's lymphoma.
2. For patients proven to be in complete remission after induction, to compare the duration of documented complete response obtained by continued maintenance immunotherapy with levamisole vs no maintenance therapy.
3. For patients with imparied cardiac function (not eligible for treatment with adriamycin), with mycosis fungoides, or with only a partial response to 11 courses of treatment with CHOP-levamisole + BCG, to estimate the complete response rate obtained by continued chemoimmunotherapy with COP + levamisole.
4. To estimate the CNS relapse rate in patients with diffuse lymphomas when CNS prophylaxis with intrathecal cytosine arabinoside is used.
5. To continue to evaluate the impact of systematic restaging of patients judged to be in complete remission and the value of expert hematopathology review of diagnostic material from all cases.
6. To establish baseline and serial data on immunologic status in both chemoimmunotherapy groups.

## METHOD

Patients with a diagnosis of non-Hodgkin's lymphoma established by biopsy with no prior chemotherapy are eligible. Patients with chronic lymphocytic leukemia are ineligible. Patients with preexisting cardiac diasease or mycosis fungoides are ineligible for the CHOP programs, but will be treated with COP + levamisole. Patients will be stratified according to nodular or diffuse histologies, adequate or imparied bone marrow reserves, presence or absence of bone marrow involvement, and performance status. Initial drug doses are based on bone marrow reserve. Treatment plans as outlined in the protocol.

SWOG 7713/14 - Stutz

## PROGRESS

(78 10 - 79 09) One patient treated for 3+ months and in complete remission.

STATUS: (O)

TITLE: SWOG 7716, Tamoxifen in Renal Cell Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO. 78/28

## TECHNICAL OBJECTIVE

To determine the response rate and survival in patients with disseminated renal cell carcinoma treated with tamoxifen.

## METHOD

Patient Eligibility: patients with histologically proven disseminated renal cell carcinoma who have received no antiestrogen agents and who have an expected survival of 8 weeks. Patients with measurable disease no longer amenable to surgery or radiotherapy who have been off all previous chemotherapy or hormonal therapy for four weeks with clearly progressive disease. Radiotherapy to the pilot lesion must have been completed 3 weeks prior to entry. Bone lesions which have received radiotherapy at anytime are ineligible.

Treatment: Tamoxifen will be given 10 mg BID orally for at least 6 weeks. If objective remission is obtained, treatment is continued until disease progression is obvious. If the lesions are static, therapy is to be continued, but reevaluation at 6-week intervals until objective remission or progression is obtained. In case of definite tumor progression after adequate therapy or severe or unusual side effects, therapy will be stopped.

## PROGRESS

(78 03 - 78 09) One patient on protocol for 2+ months with progressive disease while on treatment.

(78 10 - 79 09) No new patients were treated on this protocol. The protocol has been terminated.

STATUS: (T)

TITLE: SWOG 7717, Management of Patients with a Metastatic Adenocarcinoma of Unknown Origin, Phase II

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/17

## TECHNICAL OBJECTIVE

To determine the yeild of various diagnostic procedures in finding the site of tumor origin in patients who present with metastatic adenocarcinoma with no obvious primary source; to compare the efficacy of combination chemotherapy using fluorouracil, adriamycin, and cytoxan vs fluorouracil alone in the palliative management of patients with metastatic adenocarcinoma of unknown origin; and to assess the hematologic toxicity of the chemotherapy regimen on treated patients.

## METHOD

Patient Eligibility: histopathologic confirmation of metastatic adenocarcinoma with no obvious primary source. Patients must have measurable disease and expected sruvival of 6 weeks and have had no prior chemotherapy. The WBC must be >4000/µl and platelet count >100,000/µl.

After diagnostic studies as outlined in the protocol (para 5) to establish tumor site, the patients will be randomized to one of the following treatment schedules:

Schedule I: adriamycin, 40 mg/$M^2$, IV on day 1, q 28 days
5-FU, 1000 mg/$M^2$/day x 4 as continuous IV infusion, q 28 days
cytoxan, 400 mg/$M^2$, IV on day 1, q 28 days

If patient achieves a partial regression of measurable tumor, 5-FU administration may be changed to: 500 mg/$M^2$, IV weekly.

Schedule II; 5-FU, 1000 mg/$M^2$/day x 4, continuous IV, q 28 days.

If the patient achieves a partial regression of measurable tumor, 5-FU administration may be changed to 500 mg/$M^2$, IV weekly at the discretion of the investigator.

## PROGRESS

(78 02 - 78 09) One patient treated for 2 courses with progression of disease while on treatment.

(78 10 - 79 09) No new patients registered on this protocol. The protocol has been terminated.

STATUS: (T)

TITLE: SWOG 7719, Addition of DDP and Bleomycin to VBAP in Relapsing and Resistant Myeloma Patients. Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/09

## TECHNICAL OBJECTIVE

To evaluate the frequency, degree, and duration of response with cis-platinum (DDP) and bleomycin added to vincristine-BCNU-adriamycin-prednisone combination (VBAP) in myeloma patients who failed to respond or relapsed to combinations of melphalan and/or cyclophosphamide with prednisone (M/C+P); and to compare results with previous SWOG trials of VBAP in such patients.

## METHOD

Patient Eligibility: diagnosis of multiple myeloma with evidence of progressive disease and evidence of reasonable cardiac, renal, and pulmonary function, but no longer responding to or have not responded to M/C+P; a minimum granulocyte count of 1500 and a platelet count of 100,000 unless bone marrow studies indicate that the neutropenia and/or thrombocytopenia are due to far advanced myeloma and not myelotoxicity from previous treatment. Chemotherapy should be started simultaneously with maximum efforts to reverse all complications. Chemotherapy should not be started until the investigator is assured that the patient has recovered from prior radiation or drug induced myelotoxicity.

Stratification: M/C + P response then relapse patients
M/C + P no response patients

Treatment plan:

| DAY | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| vincristine (total) IV | 1 | | | | |
| BCNU IV mg/$M^2$ | 30 | | | | |
| adriamycin IV mg/$M^2$ | 30 | | | | |
| prednisone PO mg/$M^2$ | 60 | 60 | 60 | 60 | 60 |
| bleomycin (total) IM | | 7.5 | 7.5 | 7.5 | 7.5 |
| DDP (total) IV | | 20 | 20 | 20 | 20 |

Courses to be repeated every three weeks depending on bone marrow recovery. The interval between courses should not be greated than 6 weeks. Minimum number of courses for evaluation is 3; maximum number is 6.

SWOG 7719 - Stutz

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (T)

TITLE: SWOG 7720 - Management of Oligoblastic Leukemia

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/01

## TECHNICAL OBJECTIVE

To evaluate the efficacy of Levamisole in the treatment of acute oligoblastic leukemia in those paients with less than a 50% absolute leukemic infiltrate.

## METHOD

The investigators will collect data on the clinical course of patients with acute oligoblastic (smoldering) leukemia, a subgroup of acute leukemia patients who do not meet the requirements of the current SWOG chemotherapy protocol which requires greater than a 50% absolute leukemic infiltrate.

The investigators will compare the randomly assigned immunostimulant effect of Levamisole on half of this group of patients, as opposed to those receiving no specific treatment.

Data will be maintained on those patients in this group who subsequently attain a marrow status, which qualifies them to transfer to active chemotherapy protocols.

## PROGRESS

(79 03 - 79 09) No patients were entered on this protocol and it has been terminated.

STATUS: (T)

TITLE: SWOG 7723 - Study of Diglycoaldehyde in Adult Acute Leukemia

PRINCIPAL INVESTIGATOR: LTC Freidrich H. Stutz, MC

WORK UNIT NO: 79/05

## TECHNICAL OBJECTIVE

To evaluate the responses of adult acute leukemia to diglycoaldehyde and to study the toxicity of the drug.

## METHOD

Patients with acute leukemia will be given daily doses of digylcoaldehyde, IV, for 5 days. This treatment will be repeated at three week intervals. An adequate treatment will consist of two courses of treatment and patients will be monitored for bone marrow suppression and renal toxicity or other toxic manifestations.

## PROGRESS

(79 06 - 79 09) No patients were entered on this protocol and it has been terminated.

STATUS: (T)

TITLE: SWOG 7724, Diglycoaldehyde in Metastatic Malignant Melanoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/18

## TECHNICAL OBJECTIVE

To evaluate the response of metastatic malignant melanoma to diglycoaldehyde and to study the toxicity of the drugs.

## METHOD

Patient Eligibility: patients with disseminated disease who have relapsed or are resistant to regimens in a higher priority. Patients must have a serum creatinine $\leq$1.5 mg%, BUN $\leq$20 mg%, platelet count $\geq$150,000/mm$^3$, and WBC $\geq$4,000/mm$^3$.

Treatment: Diglycoaldehyde will be administered in daily doses of 1.5 gm/M$^2$ as a six hour intravenous infusion in 5% dextrose in water for five days. Courses will be repeated at three week intervals when possible. Second and third courses of the drug will only be administered when the WBC is $\geq$4000 and the platelet count is $\geq$150,000. No course will be commenced until any proteinuria has disappeared and until the BUN has fallen to a measurement $\leq$20 and the creatinine is $\leq$1.5. An adequate trial consists of two courses of therapy. Patients who exhibit progressive disease after two courses or who relapse from remission after two courses will be removed from the study. Patients whose BUN and creatinine remain greater than 20 and greater than 1.5, respectively, or who exhibit greater trace proteinuria for greater than five weeks post therapy will be removed from the study.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (T)

TITLE: SWOG 7725, Continuous 5-Drug Induction with Intermittent CMPF vs CMPF + Levamisole for Maintenance in Patients with Estrogen Receptor Negative Breast Cancer, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/16

## TECHNICAL OBJECTIVE

To determine the respective effects of levamisole on the duration of response and survival of patients with advanced breast cancer concurrently treated with maintenance chemotherapy after a successful remission induction trial of continuous Cooper regimen; and to accumulate data on immunologic variables under the conditions of chemotherapy alone and combined chemotherapy and immunotherapy with levamisole of advanced breast cancer.

## METHOD

Patient Eligibility: only patients proven to be estrogen receptor negative are eligible. Patients must have a life expectancy of 2 months and measurable lesions and no previous chemotherapy other than adjuvant chemotherapy. Patients coming off additive hormonal therapy and antiestrogens must have been off therapy for 6 weeks and have increasing disease. If the 6 week observation period off hormones appears to be excessively risky, the patient may be entered provided that 3 weeks have elapsed since last day of hormonal therapy and disease is rapidly progressive. Prior surgical ablative endocrine therapy must have taken place 3 weeks prior to entry if the disease is rapidly progressive and 10 weeks if slowly progressive. Patients with previous cancer immunotherapy or who had relapsed while receiving multiple durg adjuvant chemotherapy are ineligible. Concomitant therapy with mithramycin is not allowed, and concomitant therapy with corticosteroids (other than prednisone) is allowed only in adrenalectomized or hypophysectomized patients.

Treatment: All patients will undergo a remission induction trial with continuous Cooper regimen in the following fashion:

SWOG 7725 - Stutz

| | | |
|---|---|---|
| Vincristine | 0.625 mg/$M^2$ | IV once a week for 8 weeks |
| 5-Fluorouracil | 300 mg/$M^2$ | IV " " " " |
| Methotrexate | 15 mg/$M^2$ | IV " " " " |
| Cyclophosphamide | 60 mg/$M^2$ | PO daily for 8 weeks |
| Prednisone | 30 mg/$M^2$ | PO daily for 2 weeks, reduce to |
| | 20 mg/$M^2$ | PO for next 2 weeks, reduce to |
| | 10 mg/$M^2$ | until day 49, then taper to nothing by day 56 |

Patients with increasing disease after 6 weekly induction cycles will go off study. After achievement of remission or stable status, the patients will be randomly allocated to the following treatment arms:

Arm I - Maintenance "Intermittent Cooper Regimen"

| | | |
|---|---|---|
| 5-Fluorouracil | 180 mg/$M^2$ | PO daily x 5 days, q 28 days |
| Methotrexate | 4 mg/$M^2$ | PO " " " " |
| Cyclophosphamide | 120 mg/$M^2$ | PO " " " " |
| Prednisone | 40 mg/$M^2$ | PO " " " " |

Arm II - Intermittent Cooper + levamisole

The same as Arm 1 plus levamisole 100 mg/$M^2$ daily in 3 divided doses on days 4-6, 11-13, and 18-20 of each cycle.

As with all studies, dose modifications will be made when necessary.

## PROGRESS

(78 02 - 78 09) One patient was treated for eight weeks with disease progression. One patient has been on the study for one month which does not allow enough time to study for results.

(78 10 - 79 09) Three patients were treated who had increasing disease and expired. One patient was treated who had increasing disease. One patient has been treated for 1+ months with no change and one patient has been treated for 6+ months with no change.

STATUS: (O)

TITLE: SWOG 7726, Chemotherapy of Advanced Carcinoma of the Breast with Rubidazone (Phase II Study).

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/10

## TECHNICAL OBJECTIVE

To determine the efficacy and toxicity of rubidazone as determined by response rate and median duration of response in patients with disseminated carcinoma of the breast who have not received prior therapy with adriamycin or other anthracycline antibiotics alone or in combination.

## METHOD

Patient Eligibility: Patients with a life expectancy of six weeks with histologically proven advanced metastatic breast cancer who have not previously received adriamycin or other anthracycline antibiotics. Patients with symptomatic noncompensated congestive heart failure or primary myocardial disease are excluded because of possible cardiotoxicity. Patients must have been off radiotherapy or chemotherapy for four weeks prior to entering study. Prior surgical hormonal manipulation or medical hormonal therapy must have taken place six weeks before entering study. Patient must have increasing disease. Patients must have adequate bone marrow function, liver function, and renal function. Treatment with mithramycin is allowed. Adrenal steroids may be used for replacement purposes and temporarily in patients with hypercalcemia. No other chemotherapeutic agents may be given concomitantly.

Treatment 1: Good Risk

> $\leq$ 65 years of age; WBC $\geq$ 4000; platelets >150,000; no previous RT or marked tolerance to prior CT. Patients will be pretreated with benadryl 50 mg or phenergan 25 mg IV. Rubidazone 150 mg/$M^2$ IV q 3 weeks.

Treatment 2: Poor Risk

> >65 years old; WBC 2500-4000; platelets 75,000-149,000; extensive RT or marked previous intolerance to CT.

SWOG 7726 - Stutz

Rubidazone: 25% reduction (112 mg/$M^2$) for bilirubin >2 <3, or if SGOT or SGPT is >3 times normal. 50% reduction for bilirubin >3. Creatinine >2 = 25% reduction. Other "poor risk" patients will start at a 25% dose reduction.

Dose modifications and adjustments as listed in the protocol.

## PROGRESS

(78 02 - 78 09) One patient was on the study for six weeks (2 courses) with progressive disease while on treatment.

(78 10 - 79 09) No new patients were treated on this protocol. The protocol has been terminated.

STATUS: (T)

TITLE: SWOG 7727/28, Combination Chemoimmunotherapy Utilizing BCNU, Hydroxyurea, and DTIC (BHD) with Levamisole versus DTIC Plus Actinomycin-D in the Treatment of Patients with Disseminated Malignant Melanoma, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/12

## TECHNICAL OBJECTIVE

To determine remission induction rates, remission duration, survival, and toxicity in patients with disseminated malignant melanoma treated with BHD (BCNU, hydroxyurea, DTIC), BHD plus levamisole, and intermittent single high dose DTIC plus actinomycin D in a prospective, randomized clinical study.

## METHOD

Patient Eligibility: histologically proven disseminated malignant melanoma with no previous treatment with any of the agents involved; measurable disease and estimated survival of at least two months; adequate renal and hepatic function; BUN >25 mg% or creatinine >1.5 mg% and bilirubin >2.5 mg%; hepatic or renal metastases are eligible provided organ function is adequate; recovery from the toxic effects of prior therapy and completion of RT to bone marrow bearing areas at least two weeks prior to entry.

Brain metastasis treatment: decadron 8-12 mg/day x 3 PO then tapered at the discretion of the investigator; day 3 begin total irradiation, 4000 rads over 2 week period; chemotherapy or chemoimmunotherapy will begin on the second week of radiotherapy.

Hepatic metastasis treatment: hepatic artery cannulation via femoral artery or brachial artery route. DTIC 200 mg/$M^2$/day over 24 hr infusion in 1000 ml of $D_5W$ x 5 days; after 5-7 days patient will begin either chemotherapy or chemoimmunotherapy.

Patients will be stratified according to performance status and age. Treatment arms: I. (a) BHD - normal marrow (b) imparired marrow; II. (a) BHD + levamisole - normal marrow (b) impaired marrow; and III. (a) actinomycin D + high dose DTIC - normal marrow (b) imparied marrow.

If patients on BHD + levamisole or actinomycin D + DTIC have no response in the 2 initial courses, they will be crossed over. Patients not responding to BHD alone will be taken off study after an adequate trial. Dosages, courses of treatment, and

Patients not responding to BHD alone will be taken off study after an adequate trial. Dosages, courses of treatment, and modifications are given in detail in the protocol.

## PROGRESS

(78 02 - 78 09) One patient has been on the study one month. This is too soon to draw any conclusions.

(78 10 - 79 09) The above patient was treated for five months with good partial response, but was removed from the protocol due to failure in the central nervous system.

STATUS: (O)

TITLE: SWOG 7730, Cis-diamminedichloroplatinum in Refractory Disseminated Malignant Melanoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/14

## TECHNICAL OBJECTIVE

To determine the efficacy of high intermittent doses of cis-diamminedichloroplatinum in patients with advanced malignant melanoma refractory to higher priority protocols and to determine the nature and extent of toxicity of this agent with the use of IV hydration only or IV hydration and mannitol diuresis.

## METHOD

Patient Eligibility: Patients with histologically confirmed diagnosis of malignant melanoma who have not been treated with cis-diamminedichloroplatinum (CACP) before and who have an expected survival of 10 weeks are eligible for this study. Patients must have metastatic disease and measurable lesions refractory to higher priority protocols for malignant melanoma. Patients must have BUN $\leq$20 gm%, creatinine $\leq$1.7% with a creatinine clearance of at least 60 cc/min, absolute granulocyte count $\geq$2000/mm$^3$, platelet count $\geq$100,000/mm$^3$, and no evidence of obstructive uropathy as determined by IVP or renogram scan. Patients must have been off all previous chemotherapy for three weeks prior to entering the study, and the blood count nadirs must have been passed.

Treatment: Patients will be randomized to receive CACP + hydration or CACP + mannitol + hydration. Each group will receive allopurinol 300 mg PO/day started on admission to the hospital and continued as long as patient is on study; 2000 cc $D_5$ 1/2NS given IV over 24 hours one day prior to CACP therapy; an initial dose of CACP 100 mg/M$^2$ IV over 10-15 minutes; and on the day of CACP therapy 2000 cc $D_5$ 1/2NS IV plus additional IV fluids to match any emesis and continued over an additional 24 hour period following therapy. For those patients randomized on hydration only, 1000 cc of $D_5W$ over 6 hours following CACP will be given in addition to other fluids. Patients randomized to

diuresis and hydration will be given a bolus injection of 12.5 gm mannitol just prior to CACP injection and followed by 25 gm mannitol in 1000 cc $D_5W$ over 6 hours. Dose adjustments will be made as necessary. Therapy is to be repeated, until progression or relapse occurs, at 21 day intervals or delayed until there is adequate hematologic recovery.

PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (T)

TITLE: SWOG 7731, Anguidine in Adults with Advanced Soft Tissue and Bony Sarcomas

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/13

## TECHNICAL OBJECTIVE

To determine the level of efficacy of the drug anguidine as a single agent in the treatment of advanced soft tissue and bony sarcomas in patients who have failed to respond or have relapsed on other therapeutic regimens.

## METHOD

Patient Eligibility: diagnosis of soft tissue or bony sarcoma confirmed by pathologic examination of tissue; must demonstrate either primary or recurrent disease which is not amenable to control with surgery, radiotherapy, or higher priority chemotherapy; patients with prior surgery, radiation or chemotherapy are eligible if they have received no prior therapy with anguidine; patient must have measurable disease which can be followed for evidence of response; pretreatment WBC >3000/mcl; granulocytes >2000/mcl; platelets >100,000/mcl; normal hepatic function and normal renal function; patient must have been off prior chemotherapy or radiation long enough to recover from adverse effects (minimum 3 weeks); life expectancy of at least 6 weeks and performance status of at least 50% of the Karnofsky scale.

Treatment plan: all patients will recieve: anguidine 4.5 mg/$M^2$ IV over 4 hr daily for 5 days. These courses will be repeated every 3 weeks as long as disease does not progress and adverse effects permit continuation.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (O)

TITLE: SWOG 7732, The Effect of CMF With and Without Tamoxifen in Patients with Estrogen Receptor Positive Breast Cancer, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/29

## TECHNICAL OBJECTIVE

To determine if the antiestrogen, tamoxifen, in combination with Cytoxan, methotrexate, and 5-FU will alter the response rate, duration of response, and median survival seen with Cytoxan, methotrexate, and 5-FU alone in advanced human breast cancer in patients who are estrogen receptor positive.

## METHOD

Patient Eligibility: histological proof of progressing recurrent breast cancer, measurable disease, and estimated survival greater than 10 weeks. On assay of primary or recurrent tumor, estrogen receptor must be present. WBC must be $\geq$4000, platelet $\geq$100,000, hematocrit $\geq$30; patients having abnormal creatinine and BUN >30 or creatinine clearance <60 are ineligible. Patients with abnormal liver function tests must have liver scan or biopsy to diagnose liver metastasis if not previously established. Prior hormonal therapy will be allowed if it was completed 4 weeks prior to entry and there is evidence of clearly progressive disease. Glucocorticoids will be allowed as replacement therapy only after adrenalectomy. Patients with prior Cytoxan, methotrexate, or 5-FU therapy; endocrine ablation less than 4 weeks prior to entry; or radiotherapy to measurable lesion within 6 weeks of entry are ineligible. Previously radiated bone lesions may not be used as the pilot lesion.

Treatment: Patients will be randomized between CMF + tamoxifen and CMF alone as shown below:

Arm I - CMF + Tamoxifen

Tamoxifen, 10mg, BID PO daily; Cytoxan 65 mg/$M^2$ PO daily; methotrexate 15 mg/$M^2$ IV weekly; 5-FU 300 mg/$M^2$ IV weekly.

Arm II - CMF alone - the same treatment plan as Arm I without Tamoxifen.

SWOG 7732 - Stutz

Dose adjustments will be based on nadir counts.

## PROGRESS

(78 10 - 79 09) No patients have been entered on this study.

STATUS: (O)

TITLE: SWOG 7735, Anguidine in Advanced Gastrointestinal Malignancies

PRINCIPAL INVESTIGATOR: LTC Firedrich H. Stutz, MC

WORK UNIT NO: 78/30

## TECHNICAL OBJECTIVE

To determine the efficacy of anguidine and survival in terms of response rate and median duration of response in the treatment of advanced gastrointestinal malignancies; and to observe any factors predisposing to excessive myelosuppression and for other toxicities not observed during Phase I studies of this drug.

## METHOD

Patient eligibility: all patients with histologically proven gastrointestinal malignancies coming off of or not eligible for higher priority studies. Patients with life expectancy of greater than 6 weeks who have surgically incurable disease and objectively measurable parameters. Patients should not have received extensive radiation or chemotherapy within the preceding 21 days (42 days with nitrosourea). If patient has had recent surgery involving resection of gastrointestinal tract, entry should wait at least 3 weeks or until return of bowel function. Serum creatinine should be <2.0 mg%, BUN <30 mg%, and serum bilirubin <6.0 mg%. Patients with active wound infections are ineligible.

Treatment: Patients will be divided into poor risk and good risk categories; poor risk - >65 years, poor tolerance to prior chemotherapy, extensive prior radiation, serum bilirubin between 3.0 and 6.0 mg% or hepatic enzyme elevation of greater than three times the institutional normal; good risk - all other patients.

Good Risk Patients: 4.5 mg/$M^2$ (dissolved with 500 ml of $D_5W$) IV daily for 5 days.

Poor Risk Patients: 3.0 mg/$M^2$ (dissolved with 500 ml of $D_5W$) IV daily for 5 days.

Body surface area calculations will be based on ideal body weight in cases of massive obesity or ascites. Subsequent courses of treatment will be administered at intervals of 28 days as tolerated and should not be repeated until the nadir of the granulocyte and/or platelet count has recovered to at least 2,000/mm$^3$ and 100,000/mm$^3$, respectively. If after 3 days of treatment in any cycle, the WBC drops below 4,000 (granulocytes <2,000) or platelets drop below 100,000, the remaining treatment for that cycle shall not be given. Blood pressure determinations will be obtained prior to and immediately following each daily infusion. An adequate trial will consist of two courses of treatment. In the presence of tumor response or disease stabilization, courses will be repeated at 4-week intervals with any necessary dose adjustments.

## PROGRESS

(78 03 - 78 09) One patient on study for six weeks; too early for response evaluation.

(78 10 - 79 09) Patient 1 - one course, no response.
Patient 2 - 5 courses, partial response, 5 months
Patient 3 - 1 course, no response

All patients expired.

STATUS: (C)

TITLE: SWOG 7736, Evaluation of Anguidine in the Treatment of Urological Malignancies, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/31

## TECHNICAL OBJECTIVE

To determine the efficacy of anguidine in treating the major urological malignancies in terms of response rate, duration or response, and survival; to more fully study the adverse effects of anguidine and factors important in producing such effects.

## METHOD

Patient Eligibility: patients with histologically proven advanced urological malignancies not eligible for treatment with drugs of proven or likely higher efficacy with a life expectancy of at least 6 weeks. Measurable lesions are mandatory. WBC >4,000/$mm^3$, platelet count >100,000/$mm^3$, serum bilirubin <6.0, BUN <40 mg/ml, and serum creatinine <2.0 mg/dl. No radiotherapy or chemotherapy during preceding 21 days (42 days if nitrosourea) and recovered from acute toxicities of such treatment. Previous hormonal therapy in renal cell cancer is allowed, but should be stopped before entry.

Treatment: Patients will be divided into poor risk and good risk categories as defined in protocol. Anguidine must be dissolved with 500 ml of $D_5W$ and administered as an IV infusion over a period of 4 hours. The initial dose level will be as follows: Good risk: 4.5 mg/$M^2$ x 5 days
Poor Risk: 3.0 mg/$M^2$ x 5 days
Subsequent courses of treatment will be administered for 5 days at intervals of 28 days as tolerated, if the nadirs have been passed and the granulocyte count is >2000 and platelets >100,000. Dose modification will be made as required. An adequate trial of therapy will consist of one cycle of chemotherapy with evidence of increasing disease in the face of toxicity. Patients with improving disease or stable disease will continue treatment indefinitely with the proper dose adjustment.

SWOG 7736 - Stutz

## PROGRESS

(78 10 - 79 09) No patients entered on this study.

STATUS: (O)

TITLE: SWOG 7738, Combination Chemotherapy of Pancreatic Adenocarcinoma with Mitomycin-C, 5-FU, and Streptozotocin, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/32

## TECHNICAL OBJECTIVE

To determine and document the response rates and toxicity of mitomycin-C, streptozotocin, and 5-fluorouracil in the management of disseminated pancreatic adenocarcinoma.

## METHOD

Patient Eligibility: patients with histologically confirmed adenocarcinoma of the exocrine pancreas and with distant metastases and/or extension of the disease is outside of a port size >15 x 15 cm. Patients with prior exposure to mitomycin-C or streptozotocin are ineligible. Adequate renal function as evidenced by a BUN <25 mg% and a creatinine of <2.0 mg%. Patients with diabetes are eligible.

Treatment 1: Good risk - 5-FU, 1000mg/$M^2$ given as a continuous 24 hour infusion on days 1-4 and 29-32; mito-C, 15.0 mg/$M^2$ by IV bolus through a well established IV on day 1.

Treatment 2: Good Risk - 5-FU, as in Treatment 1; mito-C as in Treatment 1; streptozotocin, 400 mg/$M^2$ by IV bolus on days 1-4 and 29-32.

Treatment 3: Poor Risk - Same as Treatment 1 except mito-C starting dose will be 10.0 mg/$M^2$.

Treatment 4: Poor Risk - Same as Treatment 2 except mito-C starting dose will be 10.0 mg/$M^2$.

Dose adjustments will be made as required. A single cycle of therapy will be considered an adequate trial. Patients whose disease has remained stable or in whom a response has occurred will be continued on this regimen until progressive disease is documented.

## PROGRESS

(78 10 - 79 09) One patient was treated for one course on this protocol with no beneficial response. The protocol is complete.

STATUS: (C)

TITLE: SWOG 7804, Adjuvant Chemotherapy with 5-Fluorouracil, Adriamycin, and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/42

## TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with FAM on the disease-free interval and survival of patients with TNM stage-groups IB, IC, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

## METHOD

Patient Eligibility: patients must have TNM stage-group IB, IC, II or III gastric adenocarcinoma and no microscopic or gross residual postoperatively; no prior chemo- or radiotherapy; no medical contraindications to chemotherapy with FAM; serum bilirubin <2.0 mg/100 ml; SGOT and SGPT less than three times the upper limit of normal values; creatinine clearance >75 cc/min; BUN ≤25 mg%; serum creatinine ≤1.5 mg%; WBC >4,000; and platelets >100,000.

Treatment: After surgery, patients will be randomized to either Treatment 1 (no further therapy) of Treatment 2:
FAM - 5-FU, 600 mg/$M^2$ IV days 1 & 8, 29 & 36
adriamycin, 30 mg/$M^2$ IV days 1 & 29
mitomycin-C, 10 mg/$M^2$ IV day 1

A total of 6 courses, one every 8 weeks, will be administered. After 12 months, the active therapy phase is completed. The patient will be followed at six month intervals for five years if remission continues.

## PROGRESS

(78 10 - 79 09) No patients entered on this study.

STATUS: (O)

TITLE: SWOG 7806, Cis-Diamminodichloroplatinum (II) in the Treatment of Refractory Epidermoid Carcinoma of the Esophagus, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/35

## TECHNICAL OBJECTIVE

To determine the response rate and survival, with some degree of precision, utilizing cis-diamminodichloroplatinum II (CACP) in the treatment of patients with squamous cell carcinoma of the esophagus which is growing despite more standard therapy.

## METHOD

Patient Eligibility: Patient must have biopsy confirmed diagnosis of epidermoid carcinoma of the esophagus. Adenocarcinoma of the esophagus is not eligible. Patient must have an absolute granulocyte count of $\geq$2,000 and a platelet count of $\geq$150,000 and must be past the present nadir resulting from any prior therapy. Patient must have a BUN of no higher than 20 mg% and a serum creatinine no higher than 1.4 mg% or creatinine clearance in excess of 75 cc/minute. Two functioning kidneys and an unobstructed urinary tract are required.

Treatment: CACP 50 mg/$M^2$ IV infusion over an 1-4 hour interval, days 1 & 8 of each 28 day course. Prior to every dose, the patient must receive at least 1,000 cc of fluids above usual intake (also on the evening before administration).

As long as there is evidence of tumor regression or disease stability at an acceptable level without unacceptable toxicity the CACP will be continued indefinitely. Although 30 days on therapy will constitute an adequate tiral, an attempt will be made to give each patient two complete courses if the clinical status is acceptable.

## PROGRESS

(78 10 - 79 09) No patients entered on the study.

STATUS: (O)

TITLE: SWOG 7807, CACP in Refractory Epidermoid Carcinoma of the Lung

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/36

## TECHNICAL OBJECTIVE

To determine the response rate and survival in patients with epidermoid carcinoma of the lung who have demonstrated refractoriness to previous therapy, utilizing cis-diammino-dichloroplatinum (II) (CACP).

## METHOD

Patient Eligibility: Patients must have confirmed, preferably by biopsy, epidermoid carcinoma of the lung; an absolute granulocyte count of at least 2,000, a platelet count of at least 150,000, and must be past the nadir resulting from any prior therapy; a BUN >20 mg%, serum creatinine >1.4 mg% (if these two criteria are not met, a patient will be considered eligible if the creatinine clearance proves to be in excess of 75 cc/min); no evidence of obstruction of the urinary tract as determined by radiographic studies; and measurable disease.

Treatment: On the evening before and prior to drug administration, the patient will receive at least 1000 cc of fluids above usual intake (either IV or oral). The initial course will be given at a dose of 50 mg/$M^2$ IV infusion with the drug diluted in 1 liter D5½NS. This will be given on days 1 & 8, over an interval of 1-4 hours. The course will be repeated at four week intervals if BUN and serum creatinine and blood counts are at defined levels. For subsequent courses the drug dose will be modified based on the effects of the immediate previous course. CACP therapy will be continued indefinitely as long as there is evidence of tumor regression or disease stability at an acceptable level. Although 30 days on study will constitute an adequate trial, an attempt will be made, if clinically tenable, to maintain a patient on study for two complete courses.

## PROGRESS

(78 10 - 79 09) No patients were entered on this protocol during FY 79.

STATUS: (O)

TITLE: SWOG 7808, Combination Modality Treatment for Stages III and IV Hodgkin's Disease, MOPP #6

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/47

## TECHNICAL OBJECTIVE

To attempt to increase the complete remission rate induced with MOP-BAP (nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, and bleomycin) alone utilizing involved field radiotherapy in patients with Stages III and IV Hodgkin's disease achieving partial remission at the end of 6 cycles.

To determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when complete remission has been induced with 6 cycles of MOP-BAP in Stages III & IV Hodgkin's.

## METHOD

Patient Eligibility: Patients must have histologic diagnosis of Hodgkin's disease classified by the Lukes and Butler System; no prior chemotherapy; 15 years of age or older. Patients with a history of congestive heart failure, valvular heart disease, or serious obstructive or restrictive pulmonay disease will be excluded.

Treatment: All patients except those with prior radiotherapy must receive radiation therapy consultation before chemotherapy is started.

Treatment 1: Normal marrow patients will receive 6 cycles of MOP-BAP

Treatment 2: Imparied bone marrow patients will receive 6 cycles of MOP-BAP with dose modifications.

Complete remission (CR) patients will be randomized between Treatment 3 (no treatment) and Treatment 4 (levamisole). Partial remission (PR) patients without prior radiation therapy or residual bone marrow involvement will receive Treatment 6 (radiation therapy). PR patients with prior radiation therapy or those with residual bone marrow involvement will receive treatment 7 (4 additional cycles of MOP-BAP; after 10 total cycles of MOP-BAP, patient will continue study on MOP-BAP therapy at the discretion of the investigator). CR patients without prior radiation therapy will receive Treatment 5 (radiation therapy for CR). Doses for chemotherapy and radiotherapy can be found in para 5.0 of the protocol.

SWOG 78 08 - Stutz

## PROGRESS

(78 10 - 79 09) One patient was treated for 7+ months with excellent partial response. He was taken off the protocol because he chose to continue chemotherapy rather than go to radiotherapy as required by the protocol.

STATUS: (O)

TITLE: SWOG 7809, Maytansine (NSC-153858) Therapy of Advanced Breast Cancer, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/43

## TECHNICAL OBJECTIVE

To evaluate the effectiveness of maytansine in terms of response rate and survival in patients with breast cancer resistant to standard therapeutic modalities.

## METHOD

Patient Eligibility: Patients with histologically proven breast cancer resistant to known effective agents; expected survival of 6 weeks; either disease progression on prior therapy or have received no hormonal or chemotherapy or radiation therapy to the measurable lesion for at least 4 weeks; and measurable disease. Patients having received prior vincristine therapy will be analyzed separately.

Treatment I: Good Risk Patients: 0.5 mg/$M^2$/day x 5 days IV every 21 days

Treatment II: Poor Risk Patients: 0.3 mg/$M^2$/day x 5 days IV every 21 days

Poor risk defined as patients with liver metastasis or abnormal liver function.

Drug dosage will be increased every other treatment as outlined in para 5.0 of the protocol.

Duration of treatment: (1) terminated if increasing disease after two courses of therapy; (2) terminated if severe or life-threatening toxicity; (3) terminated upon relapse; (4) terminated if stable disease after three courses of therapy at physician's discretion.

## PROGRESS

(78 10 - 79 09) No patients entered on study, and it has been terminated.

STATUS: (T)

TITLE: SWOG 7811 - Brain Metastases Protocol, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/03

## TECHNICAL OBJECTIVE

To determine the effectiveness of combined radiation therapy and metronidazole (Flagyl) in the treatment of patients with brain metastases from primary malignancies outside the central nervous system, compared with radiation therapy alone, as determined by objective response (brain and/or CAT scan) and/or increase in functional neurologic level and duration of response.

To determine the toxicity of multiple dose administartion of metronidazole and radiation therapy.

## METHOD

Patients will have had no prior radiation to the brain. Patients with brain metastases will be treated with whole brain irradiation therapy. A second group will be treated with whole brain irradiation therapy plus metronidazole.

## PROGRESS

(79 03 - 79 09) One patient was entered on this protocol, but was withdrawn in a short period of time due to an inability to tolerate the medication.

STATUS: (O)

TITLE: SWOG 7814, A Comparison of Methotrexate and Cis-Platinum for Patients with Advanced Squamous Cell Carcinoma of the Head and Neck Region

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/46

## TECHNICAL OBJECTIVE

To determine whether cis-platinum will give a superior response rate and/or a longer remission duration than methotrexate in patients with squamous cell carcinoma of the head and neck region. SWOG 7814 combines the two best treatments of previously approved SWOG protocols, 7519 and 7629, which it replaces.

## METHOD

Patient Eligibility: patients with histologically proven advanced squamous cell carcinoma of the head and neck region which is not amenable to other forms of therapy and with measurable tumor lesions; no prior methotrexate or cis-platinum therapy; objective evidence of disease progression 3 weeks or more after discontinuation of any prior radiotherapy or chemotherapy; life expectancy of 8 weeks or more; creatinine clearance of $\geq$50 cc/1.73 $M^2$/min; WBC of $\geq$4,000, platelets >125,000, and optional bone marrow biopsy to assess adequacy of bone marrow reserve.

Patients will be randomized to receive either:

Treatment 1: methotrexate alone, 15 mg/$M^2$ IM daly x 3 days, every 3 weeks
Treatment 2: cis-platinum alone, 50 mg/$M^2$, days 1 & 8, every 4 weeks

Adequate treatment: patients must receive two complete cycles of therapy showing some biological activity from the drug. Patients will be removed from study if: increasing disease following the initial treatment cycle or the second cycle as manifested by at least Grade 2 toxicity. Patients with no change in their measurable disease may be continued on study at the discretion of the investigator. Patients will be removed from study following progression of disease.

## PROGRESS

(78 10 - 79 09) No patients entered on study.

STATUS: (T)

TITLE: Treatment of Advanced Germ Cell Neoplasms of the Testis: Remission Induction with Vinblastine, Bleomycin, with Low-Dose or High-Dose Cis-Platinum; Surgical Removal of all Residual Tumor Following Remission Induction; Maintenance Therapy with CTX, Actinomycin-D, Adriamycin and Vinblastine, Phases II-III. SWOG 7817.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/04

## TECHNICAL OBJECTIVE

To determine in a randomized fashion the effectiveness of cis-platinum given in the conventional low-dose schedule daily x 5 days vs high-dose intermittent treatment in remission induction of disseminated testicular cancer, when combined with vinblastine and bleomycin.

To determine the survival of patients who achieve a partial remission and are rendered disease-free by surgical removal of residual disease and maintained on the same chemotherapy as patients who achieved complete remission status on chemotherapy alone.

To determine the effectiveness of cyclophosphamide, actinomycin-D, adriamycin, and vinblastine, in the maintenance of remission status.

To document the nature and extent of the hematologic and non-hematologic side effects of the various drug combinations.

## METHOD

Patients with carcinoma of the testis will be treated randomly with cis-platinum utilizing the low dose schedule vs the high dose intermittent treatment when combined with vinblastine and bleomycin. These patients will then be maintained on cyclophosphamide, actinomycin-D, adriamycin, and vinblastine.

## PROGRESS

(78 11 - 79 09) No patients have been entered on this protocol.

STATUS: (O)

TITLE: SWOG 7823/24/25/26 - ROAP-AdOAP in Acute Leukemia, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/02

## TECHNICAL OBJECTIVE

To compare the efficacy of the 4-drug combination chemotherapy regimen, ROAP (Rubidazone, Vincristine, Arabinosyl Cytosine, and Prednisone) to AdOAP (the same combination using Adriamycin in place of Rubidazone) in adult acute leukemia, as determined by remission duration and survival.

To determine the comparative toxicity of these regimens.

To determine whether late intensification therapy at 9 months after complete remission will improve long-term, disease free survival.

To determine whether immunotherapy using Levamisole for 6 months after 12 months of complete remission on chemotherapy improves disease-free survival.

To determine the effects of intrathecal Ara-C on the incidence of CNS leukemia.

To determine reproducibility of the FAB/histologic classification and correlation to response to therapy in 200 consecutive cases of acute leukemia.

To study the effects of intensive supportive care in the management of acute leukemia.

## METHOD

For remission induction Group A will receive ROAP and Group B will receive AdOAP. When leukemic cells are no longer visible in the bone marrow consolidation therapy will begin with one-half the patients receiving only chemotherapy consisting of the same drugs , but in reduced dosage. The other one-half will receive the same drugs with the addition of cytosine arabinoside in the spinal fluid at weekly intervals for 8 weeks. If a complete remission persists, maintenance therapy will be given consisting of vincristine, cytosine arabinoside, and prednisone for 5 days at monthly intervals for 9 months. One half of these patients will then receive late intensification

therapy consisting of a combination of vincristine, prednisone, and methotrexate, and 6-mercaptopurine for 5 days. The other one-half will receive 3 additional months of maintenance therapy, at which time all patients will be randomized into one group receiving no further treatment and another group receiving levamisole for 2 days of each week for 6 months.

PROGRESS

(79 04 - 79 09) Two patients have been entered on this protocol.

Patient 1: expired after 5 months of treatment.

Patient 2: on protocol one month; too soon for evaluation.

STATUS: (O)

## APPENDIX I

## GUIDING PRINCIPLES OF THE CARE AND USE OF ANIMALS

Approved by the Council
of The American Physiological Society

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort; they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

## APPENDIX II

### Recommendations from the Declaration of Helsinki

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.

3. a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

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